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VOL. II.—42ND YEAR SYDNEY, SATURDAY, NOVEMBER 26, 1955 No. 22

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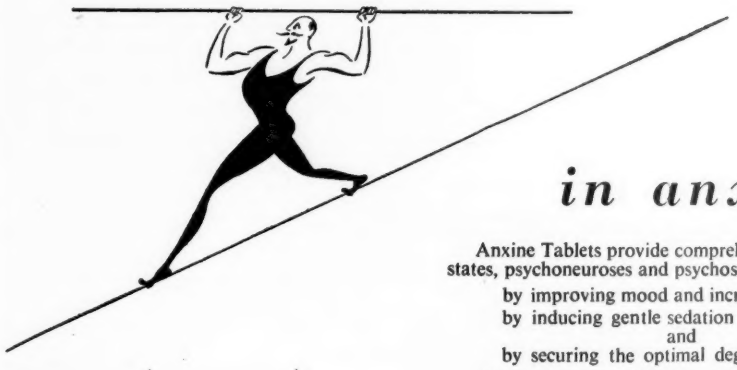

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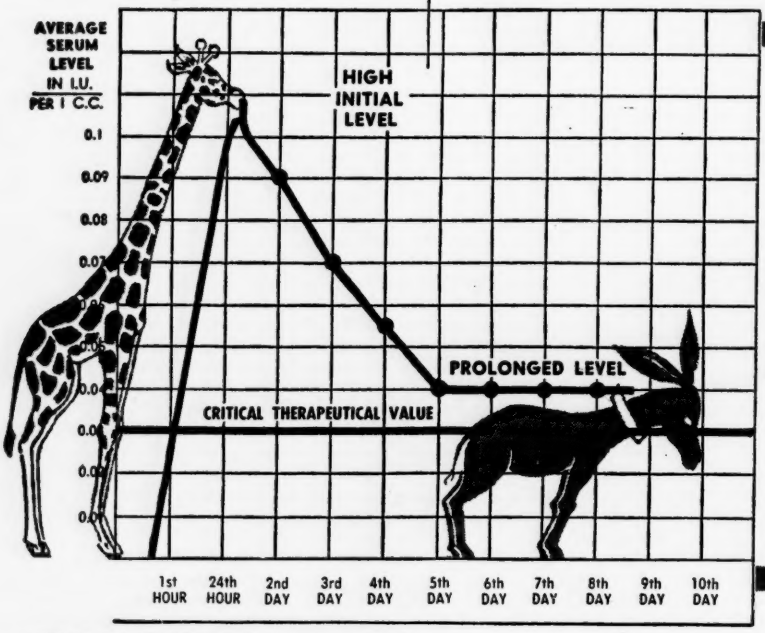

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The Joseph Bancroft Oration.[1]

THE WORLD MEDICAL ASSOCIATION AND ITS RELATION TO MEDICAL PROGRESS.

By LOUIS HOPEWELL BAUER, A.B., M.D., F.A.C.P., F.A.M.,
Secretary-General, The World Medical Association.

IT is a great privilege and honour to deliver the Joseph Bancroft Oration today.

Having entered the United States Army Medical Corps early in my medical career, it became necessary for me to study tropical medicine. Hence I became acquainted early with the name of Joseph Bancroft.

He seems to have been a man of extraordinary accomplishments, Besides discovering the *Filaria bancrofti*, he was both a physician and a surgeon. In his era it was, of course, possible for one man to know almost all there was to be known in medicine. Dr. Bancroft, however, was not content to confine his investigations entirely within the field of medicine. He delved into botany and agriculture. Among the 100 varieties of wheat he grew on his experimental farm he discovered a rust-proof variety, which could be grown in his section of Australia. Conditions are different today. A doctor not only cannot know all there is to know about medicine; he has difficulty in knowing all there is to know about one special field of medical science.

For centuries medicine was hamstrung by ignorance and superstition. Yet as early as 500 B.C. we find the glimmerings of science. It was not, however, until the first human body was dissected that progress began. Growth continued slowly for the next 300 years. In the middle of the nineteenth century medicine was still largely an art and included little science.

With the discovery and development of anæsthesia and bacteriology progress really began. From the beginning of the twentieth century on, tremendous strides have been made. Science outstripped the art in the practice of medicine.

Medicine is on the march, constantly searching for new and better methods that will alleviate or eradicate the ills of humanity. To the best of my knowledge the medical profession is the only one that is striving constantly to eliminate the necessity for its own existence. To prove

[1] Delivered at a meeting of the Queensland Branch of the British Medical Association on August 29, 1955.

this statement one has only to recall the diseases which have all but disappeared or have been brought under such control that their names no longer strike terror.

Until recently, problems in medicine were largely local, or at least while problems existed the world over, no one thought much about attacking them on a world basis.

Spasmodic and scattered attempts in the latter part of the nineteenth and early part of the twentieth centuries were made by medical missionaries. Even these attempts, however, were largely local and not very effective.

With the development of the former League of Nations some progress was made through its Health Organization. The League and its Health Organization, however, disappeared before the Second World War.

Following the last war, the United Nations was organized and, in 1948, the World Health Organization was established as its health agency.

Being a governmental organization and supplied with government funds, the World Health Organization has accomplished considerable in attacking epidemics and eradicating diseases in various parts of the world. It has engaged in multiple other activities, not always, I feel, strictly within its province. It must be remembered that the World Health Organization, being governmental, has a governmental viewpoint and its delegates are not always doctors and the medical experience of many of those who are doctors is limited to the field of public health. Hence the World Health Organization cannot and does not represent either medicine or the medical profession, but only governments.

A year before the World Health Organization became fully established The World Medical Association was organized. The World Medical Association is an organization of national medical associations and, therefore, does represent the medical profession and, through it, medicine. There are now 50 national medical associations comprising its membership. Its purposes are to effect a better liaison among the doctors of the world; to serve as a forum for discussion of medical problems; to protect the interests and traditions of medicine; to distribute information; to raise standards in medical education, medical care and health; to represent the medical profession before other international bodies; and to better international relations.

The World Medical Association is not primarily a scientific organization, but rather what the continental European would call a professional organization. In other words, it is primarily interested in the socio-economic problems of medicine, in medical education, and medical journalism. It has, however, a scientific session in conjunction with its annual general assembly and publishes general articles on scientific advancements in its journal.

A half-century ago there were few socio-economic problems besetting the medical profession. Of course, in 1883, Bismarck started the snowball of compulsory health insurance rolling down hill. Bismarck's action was primarily a political one and, unfortunately, the whole system of compulsory health insurance continued to be increasingly political. Eventually it became tied in with social security, with the result that social security also became tainted with politics.

Economic conditions, of course, differ in different parts of the world. What is necessary or advisable in one area is unnecessary in another. If social security is essential for those who are unable to help themselves either temporarily or permanently, that is one thing; but if that be so, then countries economically well situated should need less of it.

Yet the whole philosophy of the social security promoters is that of the Welfare State. Governments, according to these individuals, should do everything for the citizen. The citizen should feel no responsibility for himself or his family. There is no need, according to these planners, to provide for one's old age. Let the government do it. If one becomes ill, let the government furnish the medical care. According to these socialistic-minded bureaucrats, the State is the supreme master and the citizen the servant. Their philosophy absolutely negates the democratic principle that the State is the servant of the people.

Your country, Canada and my country have been freer from such philosophy than any others, but we, too, have had to combat such a philosophy.

In the United States there was a period during which we were slipping down the socialistic toboggan slide very rapidly. Now this tide has been stemmed to a certain extent. You also, in Australia, have had a taste of it. Today you are fortunate in that you have a Health Minister, the Right Honourable Sir Earle Page, who is a doctor, who has not forgotten that he is a doctor, and who respects the opinion of the medical profession. Not every country is so fortunate as that. Too often health is a political football. Politicians make promises, forgetting that the fulfilment of promises costs money. When they cannot carry out these promises they blame the medical profession. They hold out a Utopia to the public and the public naturally holds out its arms to receive it. So far as I know, however, Utopia never has existed and probably never will exist outside of the feverish minds of certain wishful thinkers.

As if it were not difficult enough for us to combat the activities of the nationalizers and socializers in our own countries, we are now faced with protecting ourselves from inroads by their international agencies.

I should like to bring to your attention two of these organizations which I consider of great danger to medicine and medical progress.

The first is the International Labour Organization. This has existed since 1919 and is now an agency of the United Nations, with headquarters in Geneva. It is an intergovernmental agency of 69 countries representing governments, labour and employers.

It is intruding more and more into the medical field. Nevertheless it has never sought the opinion of the medical profession on medical matters, but only the opinions of governments and governmental agencies. Any doctors it employs are in subordinate positions, and even in strictly medical matters a layman decides technical procedures and answers correspondence.

This organization believes in compulsion and has adopted a convention calling for compulsory health insurance or government-controlled voluntary insurance for all people receiving medical care under social security. Its aim is to include the whole population under a compulsory medical care programme.

Its technical assistance programme has been tremendously expanded. Originally, it was limited to working conditions, manpower and industrial relations. Now it includes complete medical care under social security with the employment of so-called "experts". In 1952 it refused to present to the delegates at its annual convention a statement from The World Medical Association giving the viewpoint of the medical profession as to medical care under social security systems. Instead it presented a report compiled by a committee appointed by the World Health Organization, on which there was not a single practising doctor. The report was an insult to the entire practising medical profession.

Russia has now returned to the fold of the International Labour Organization and has stated it is returning to the World Health Organization. This is most unfortunate, for, through the technical assistance programmes of both organizations, Russia, by means of its own "experts", will undoubtedly endeavour to infiltrate its communistic philosophy into governments, especially those of the underdeveloped countries.

The philosophy of the International Labour Organization and its increasing intrusion into medical matters make it a direct threat to the freedom of medicine and to progress in medical science. Its one aim is complete socialization of every country.

The other organization to which I wish to direct your attention is the International Social Security Association. This association is closely allied to the International

Labour Organization, which furnishes its secretariat. Its Secretary-general is appointed on the recommendations of the Director-General of the International Labour Organization.

The philosophy of the two groups appears identical in most phases.

The International Social Security Association likewise has ignored the medical profession and has never made any effort to obtain the opinion or guidance of practising doctors.

In 1953 it adopted 15 conclusions with reference to medical care under social security. The World Medical Association had asked for a conference with this organization to discuss mutual problems. The International Social Security Association refused such a conference unless and until The World Medical Association commented on these 15 conclusions. The latter were in many cases so vaguely worded that no comment was possible. Finally, after using delaying tactics for nearly two years, the International Social Security Association has agreed to a conference.

Statements by some of this organization's spokesmen indicate that the ultimate aim of the International Social Security Association is to place doctors on the status of labour technicians and employ them as full-time salaried servants of the social security bodies; to abolish free choice of physician; to deny the doctor the freedom to choose the place and type of his practice, even importing doctors from other countries if necessary; to limit the doctor in his therapeutics; to establish diagnostic and treatment centres under lay control; and even to modify medical education, so that the future doctors will be thoroughly inculcated with the social security philosophy. In fact, the organization is on record as stating that collaboration with the doctors is possible only if the medical profession adopts as its own the principles on which social security is based.

Have I said enough to impress you with the fact that there are international problems in medicine that cannot be handled solely by national medical associations? These problems require the support of all national medical associations through an international organization of their own. No wonder that it was said recently that were there not now a World Medical Association one would have to be organized immediately.

The World Medical Association is not only concerned with protecting the rights of medicine and doctors. Its primary concern is in maintaining high standards of medical care and protecting the public.

One of its earliest acts was to adopt the Declaration of Geneva, which is an up-to-date version of the Hippocratic oath. This was primarily the result of commission of medical war crimes by certain doctors during the Nazi régime.

In the time of Hippocrates no one ever dreamed that doctors would ever let race, religion or politics intervene between their duty and their patients. No one ever imagined that doctors, even under threat, would ever use their medical knowledge contrary to the laws of humanity. Hence the Declaration of Geneva was composed to cover such eventualities.

Out of this grew the International Code of Medical Ethics. Upon investigation it was found that some countries did not have a national code of medical ethics, but that where codes did exist they were very similar. The International Code is and must be general and fundamental. Details may be added by the profession to fit the national needs of each individual country.

If the public is to receive the best we have in medical care, if we are to foster advances in medical science, medicine must be kept free and on an individual basis. This cannot be the case if we stifle competition, foster assembly line medicine or destroy initiative.

Your own Health Minister, the Right Honourable Sir Earle Page, has summed this up in a few words:

> The healing of the sick is a personal and individual matter, one between doctor and patient. It cannot be done *en masse*. Regard must be had for individual idiosyncrasies. All sorts of psychological factors enter into a cure for each individual.
>
> Sickness is a vitally personal and individual matter to each sick man, woman or child. Each human being has different allergies. No disease runs an exactly similar course in every person. Its course is determined by the constitution, heredity, previous diseases and condition of other organs.
>
> It is obvious, therefore, that human disease cannot be overcome by mass treatment. Successful treatment of the individual will not be effected merely by the exhibition of a stock drug or some set formula of treatment.
>
> Successful treatment lies in the cumulative effect of confidence in doctor, exact diagnosis, efficiency of treatment, wise and balanced use of various therapeutic measures and consideration of the patient's general condition. Retenton of the self-respect of the individual and pride in his independence helps all these. These factors always applied and always will.

The World Medical Association is your voice in these matters at the international level. There is no other organization that expresses the ideals and opinions of 700,000 practising doctors.

Besides fighting battles to protect the freedom of medical practice, your Association is working on other fronts. One of these is medical education. It sponsored the First World Conference on Medical Education in London in 1953. Out of this conference came much food for thought. Methods in use in different areas of the world were compared; opinions were shared; arguments ensued and everyone present felt that a great stimulus had been given to the advancement of medical education.

As Sir Richard Livingstone said so pointedly, we must seek in education a philosophy of life which involves the "first rate". He said:

> An educated man knows and an uneducated man does not know what is first-rate, and the best educated man is he who knows the first-rate in the most important human activities . . . . To repeat, an education which leaves us without a philosophy of life is as incomplete as one which leaves us unable to think or express our thoughts.

The proceedings are now being studied and the results of these studies will culminate in a Second World Conference in 1959.

Occupational health services is another programme in which the World Medical Association is endeavouring to assume leadership and coordinate activities. An international committee has been appointed and a general programme outlined. At present a survey is being made of the actual status of occupational health services in the various countries. Effort will be made to acquaint the man in general medicine with some of the basic principles of occupational health.

Still another project of The World Medical Association is its programme to develop an emblem and have it recognized as a means of protecting medical units and personnel engaged in civil defence, just as the Red Cross protects such units and personnel attached to the armed forces. Other activities include a study of the feasibility of establishing a central repository for medical credentials to prevent their complete loss during war or disaster, and protection of the rights of medicine and doctors in the attempt being made to draft a code of international medical law governing the activities of doctors in both peace and war.

Facilitation of travel of doctors from one country to another, planning of lectures, assistance in training of doctors from under-developed countries in the more developed ones, all tend to improve standards, bring about better liaison among the members of the profession, and help to improve international relations.

The World Medical Association publishes *The World Medical Journal* bimonthly. This journal, published in the three official languages—English, French and Spanish—endeavours to present medical news, both scientific and organizational, from all over the world. It also portrays

the activities of the Association. It is still in the evolutionary stage and welcomes critical comments for its improvement so that it may become an international voice for the medical profession.

You, owing to the efforts of Dr. L. R. Mallen, your distinguished member of our Council, and Dr. J. G. Hunter, your distinguished secretary, have formed in Australia a supporting committee for The World Medical Association. All members of this committee receive or should receive this journal. Your Association is in the van of those national member associations that are using every effort to advance the effectiveness of The World Medical Association. I am happy to say that the Federal Council of the British Medical Association in Australia is one of the most forward-thinking of our member associations.

Medicine is a universal language. Doctors have much the same philosophy, no matter whence they come. I have often said that more doctors should enter the diplomatic field. I believe that doctors through their contacts in The World Medical Association have succeeded better than any other group in improving relations between countries.

Doctors have, however, been derelict in their own public relations. They must come out of their ivory towers and foster good relations with the lay Press and with the public. The World Medical Association is working in this direction also.

Doctors have from time immemorial considered medicine a public service. The doctor who looks on medicine merely as a means of making a living is not a credit to the profession and, I am glad to say, there are not many of this type.

We of the medical profession owe it to the public to take them into our confidence and explain many things they need to know. Medicine has passed out of the empiric stage with prescriptions written in Latin, and in fact has progressed beyond the mere curative phase. Preventive medicine has become equally important — perhaps more important, for who would deny that it is better to prevent disease than to cure it?

We need the help of the public and of health agencies. While the doctor-patient relationship remains ever important, medicine is no longer just an individual affair. It involves health departments, dentists, nurses, laboratory technicians, physiotherapists, social welfare agencies and others. All this requires the cooperation of the public. The public needs to know the importance of early detection of diseases like cancer and diabetes; the importance of after-care in such diseases as rheumatic fever; what can be done in the way of inoculation against preventible diseases, like smallpox, yellow fever, cholera *et cetera*; the dangers of self-medication. Where should the public go to get this information except from the doctor? Lay organizations are not competent to give it. The public must be given an opportunity to understand that there are reasons for certain medical attitudes, and that these attitudes are in the interest of the public. Else we may have the situation described by Rhazes, the famous Arabian physician, who said:

> The public demands that the physician should cure in a moment, like a magician, or that he should at least employ pleasant methods, which is not at all times and in all cases possible; to blame the physician on nature's account is a great injustice. Thus it is that sorcerers make their fortune, even though they behave iniquitously, and their incompetent work brings them a good livelihood, while the physician must often endure poverty.
>
> The heart of the public is further turned from the capable physician and towards fools because the ignorant sometimes succeed in curing complaints where this had not been done by the most famous physician. The causes are manifold, luck, opportunity, etc. Sometimes the qualified physician effects an improvement which is not, however, yet visible; the patient is then placed under another doctor who rapidly brings about a cure and obtains the entire credit.

I believe it should be quite evident that the activities of The World Medical Association which I have described have a distinct relation to medical progress. Improving standards in medical education and medical care; development of a programme in occupational health; protecting the freedom of medical practice, including the free choice of doctor and maintaining the doctor-patient relationship; improving relationships between the medical and lay Press; advancing health education of the public; and, in general, improving the public relations of the medical profession and of medicine with the public, are all bound to be reflected in the progress of medical science to which we are all devoted.

Government has played an increasing role in medical affairs. In some cases this is necessary—for example, in public health and in care of the mentally ill. This does not mean, however, that government should take over medical care *in toto*. In my opinion, this would be a tragedy.

In the United States the medical profession has come to accept the principle of the prepayment of medical care, but on a voluntary insurance basis. You here in Australia have turned to the voluntary method, although your system is different from ours. This, however, only illustrates what I have said in substance before—that what is the answer in one country may not be the answer in another.

I believe, nevertheless, that our countries are sufficiently alike in their philosophy to permit me to quote what I once told a group of American doctors as to the future of medicine:

> For the future, I suggest that we may look forward to extension of public health coverage with participation of local government in that field, extension of hospital and diagnostic facilities with perhaps more interlocking with large medical centres, a better balance between general practice and specialization, extension of prepaid hospital and medical care insurance on a voluntary basis, and the development of community responsibility in health problems with all agencies interested in health forming a community health council.
>
> Health and medicine are no longer individual affairs. There must be teamwork among all individuals and agencies. Each has his proper place in the team. The physician must be captain of the team and lead the way to better health. No longer can he devote himself entirely to so-called curative medicine. He must be familiar with preventive medicine, social medicine, and medical economics. He must educate the public. No one can take his place nor offer the advice nor afford the leadership which he is competent to provide.

Unless we can succeed in maintaining high standards in medicine, unless we can keep politics out of medical science, and unless we can maintain the independence of medicine, not only will it deteriorate, but persons of high character and good education will no longer be attracted to it. It is a challenge which we must meet.

Again, to quote Sir Earle Page:

> The challenge, therefore, is thrown out to the medical profession of the world and to every modern society as to how the health of the nation can be improved, the standard and quality of medical practice raised, and modern equipment and adequate hospital accommodations made available to permit advantage being taken of our great advances in knowledge, yet keep the cost within the means of the people.
>
> If initiative and intelligence can satisfactorily answer this challenge, the best minds of the community will be attracted to the healing art, and the future of medicine and medical practice assured.

Before closing may I give a text to every doctor in the world?

Think in terms of today, not yesterday. Be progressive, not reactionary. Do what you can to keep medicine in the forefront and see that everyone gets the benefit of it. Be a forward-looking physician, but above all be a citizen who is interested not only in the welfare of medicine but in the welfare of his country.

Having opened my remarks by referring to a famous Australian physician, I should like to close by quoting a famous Englishman, Rudyard Kipling. While he wrote his "Recessional" with something quite different in mind, I believe it applies to our present-day situation in medicine. I shall quote the three stanzas that are most applicable:

God of our fathers, known of old,
Lord of our far-flung battle line,
Beneath whose awful Hand we hold
Dominion over palm and pine—
Lord God of Hosts, be with us yet,
Lest we forget—lest we forget!

The tumult and the shouting dies;
The Captains and the Kings depart;
Still stands thine ancient sacrifice,
An humble and a contrite heart.
Lord God of Hosts, be with us yet,
Lest we forget—lest we forget!

Far-called, our navies melt away;
On dune and headland sinks the fire:
Lo! all our pomp of yesterday
Is one with Nineveh and Tyre.
Judge of the Nations, spare us yet,
Lest we forget—lest we forget!

THE USE AND ABUSE OF BLOOD TRANSFUSIONS.[1]

By KEVIN FAGAN,
Sydney.

In surgical practice the chief indications for blood transfusions are hæmorrhage, severe trauma and burns.

Hæmorrhage.

It is in the treatment of acute hæmorrhage that the most dramatic benefits of blood transfusion are seen. Good results depend on giving the blood in the correct amount and at the correct rate. It is always difficult to estimate even approximately the amount of blood lost in hæmorrhage. As a rule, the only guide is the clinical state of the patient. Variations in individual responses to blood loss, and the compensatory mechanisms available to the circulation, render clinical signs disconcertingly variable. Those who are experienced in resuscitation recognize the clinical state of hæmorrhagic shock in its various degrees of severity at a glance, and by a rapid examination of the patient's skin and pulse. To those of us who are not frequently faced with the problem of acute hæmorrhage, some help is available from the studies of Wallace and Sharpey-Schafer (1941), of Poles and Boycott (1942), and of Howart', and Sharpey-Schafer (1947) on the effects of bleeding volunteer donors. In healthy adults, loss of 0·5 litre of blood produces nothing more serious than a 5% incidence of vasovagal attacks; sudden loss of 1·0 litre may produce no symptoms or signs, or it may produce an unstable circulatory state in which change of posture from the lying to the sitting position will cause a fall of blood pressure with or without fainting; sudden loss of 1·5 to 2·0 litres produces the clinical picture of hæmorrhagic shock; sudden loss of 2·5 litres produces severe hæmorrhagic shock and is likely to be fatal without treatment.

Grant and Reeve (1951) found that the systolic blood pressure was the most useful single guide to the amount of blood loss in battle casualties. They found that a systolic blood pressure of less than 100 millimetres of mercury indicated a blood loss of at least 1·5 litres in a recently injured patient about to undergo resuscitation.

Profuse sweating, with the other signs of hæmorrhagic shock, indicates a blood loss of at least 1·5 litres.

These findings are of some help in estimating the amount of a single sudden loss of blood. However, in practice one is more often concerned with a patient who has lost blood, and is either still bleeding or likely to resume bleeding, and who must be operated on. If blood loss has been sufficient to be reflected in the patient's blood pressure, in the rate and quality of the pulse, and in the state of the peripheral circulation, transfusion is necessary, especially if further bleeding is possible. The administration of serum or dextran will resuscitate the patient; but only blood can provide the minimum safe level of hæmoglobin in the blood for anæsthesia (nine to 10 grammes *per centum*), and only blood can prevent prolonged anæmia during recovery, with lowered resistance to infection. The blood must be given promptly and at a rapid rate, if necessary by two or more veins, and if necessary under pressure. The amount of blood to be given, and the rate at which it is to be given, will be determined by the clinical response of the patient. It is not wise to be guided by the blood pressure alone, because it is frequently found that the blood pressure rises to apparently satisfactory levels long before the blood volume is restored. The transfusion should be continued until the patient's skin is warm and dry, the pulse is of good volume, and the blood pressure is over 100 millimetres of mercury, systolic. If improvement is not manifest after the transfusion of a litre of blood, continued bleeding must be presumed and operation proceeded with. Any patient who has been involved in an accident may have a ruptured spleen or other source of intraabdominal hæmorrhage.

When the source of bleeding cannot readily be controlled, or when hæmorrhage can reasonably be expected to cease spontaneously—for example, gastro-duodenal hæmorrhage—circulatory depression is a factor in the spontaneous cessation of bleeding. Rapid resuscitation is therefore indicated only as a prelude to operation.

Trauma.

We recognize "shock" in a patient who has cold, clammy extremities, rapid thready pulse, and a low systolic blood pressure. This clinical state arises from a disparity between the capacity of the vascular bed and the circulating blood volume. The circulating blood volume may be diminished by hæmorrhage, burns or unreplaced water and electrolyte losses. The capacity of the vascular bed may be increased by severe toxic states such as general peritonitis or septicæmia, or by widespread vasomotor paralysis. Grant and Reeve (1951) found that blood loss accounted for the main phenomena of "wound shock". In acute trauma "shock" means blood loss. This is of special importance in abdominal injuries.

The blood loss may not always be apparent. Clarke, Topley and Flear (1955) have estimated the blood loss in patients with closed fractures of long bones, by observing the increased limb volume and the cell volume deficit four days after the injury. They measured losses of 0·5 to 1·0 litre in cases of major closed fractures, and in cases of multiple open fractures losses of up to 4·0 litres. In severe fractures of the pelvis, even without visceral injury, losses of two to three litres were found. Prentice *et alii* (1954), reporting on the use of blood in the Korean war, emphasize the large losses of blood associated with extensive wounds of muscle. Both these groups of workers noted that the majority of the patients studied had received less than their theoretical requirements of blood.

Pre-operative Transfusions.

Blood transfusion may be required as part of the preoperative treatment, to restore the hæmoglobin level. Such transfusions are best given as packed cells. In patients with normal blood volumes, pre-operative transfusions should be completed at least twenty-four hours before the induction of anæsthesia. Substantial increase in the blood volume immediately before or during an anæsthetic may add to its danger, especially in patients with diminished cardiac reserve.

The amount of blood required may be calculated approximately. The number of grammes *per centum* by which one litre of blood will raise the hæmoglobin content is obtained by dividing the figure 24 by the patient's body weight in stones; and when packed cells are to be used, by dividing the figure 60 by the body weight in stones.

Transfusions during Operation.

The amount of blood lost during operations has been measured by various workers. It has been found that in the common general surgical operations such as appendicectomy, herniorraphy, cholecystectomy, mastectomy and thyroidectomy, the loss varies from 25 cubic centimetres

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on June 30, 1955.

in appendicectomy to 600 cubic centimetres in difficult thyroidectomy. Such losses do not justify the routine use of blood transfusions during such operations.

When an operation is likely to be prolonged, or when the anatomical situation involves the risk of sudden severe bleeding, it is necessary to have a transfusion running slowly before or early in the course of the operation. This applies to operations such as a difficult gastrectomy, resection of the rectum, and operations of similar magnitude. In operations on or near the great vessels, a wide-bore cannula should be tied into a vein and blood run in slowly before the operative field is exposed.

In the estimation of the need for blood during operation, the surgeon and anæsthetist should collaborate. The anæsthetist estimates the requirements by the clinical state of the patient, and by the pre-operative hæmatological and circulatory status of the patient. The surgeon is better able to judge the amount of blood lost and likely to be lost.

Burns.

In some centres, blood is given during the resuscitation of patients with an appreciable area of deep burn. In this country, and in the United Kingdom, blood is not usually given during the period of shock and hæmo-concentration —that is, during the first forty-eight hours. However, blood is necessary to correct the anæmia which often develops towards the end of the first week in cases of severe burns, to replace blood lost during operative excision of sloughs, and during subsequent reparative procedures.

The Risks of Blood Transfusion.

Blood transfusion has a mortality equivalent to that of appendicectomy (Unger, 1954). In London there is one death attributable to transfusion for every 13,000 bottles of blood used (Consulting Pathologists' Group Committee Report, 1953). These facts should be remembered by every doctor who orders a blood transfusion. The attitude of mind implied in the statement "we have the blood, we may as well give it" is to be deprecated. The need of the patient for blood must be weighed against the danger of a transfusion.

The commonest undesirable effect of a transfusion is the pyrogenic reaction. The severity varies from a mild rise in temperature to a rigor. The fever usually occurs within one and a half hours of a rapid transfusion, or during a slow one. It is usually more alarming than serious, but for a very sick patient it may be not only unpleasant but dangerous, especially immediately before operation. The commonest causes of the pyrogenic reaction are imperfect cleansing of the giving sets, and the use of other than freshly distilled water for the final washing of the giving sets immediately before autoclaving.

Allergic reactions sometimes occur. They add to the patient's discomfort, but rarely to his danger.

There are three serious complications of blood transfusion—namely, hæmolytic reactions, the transmission of disease, and circulatory overload.

Hæmolytic Reactions.

Hæmolytic reactions are very rare. They are due to the administration of blood which is either incompatible or has undergone hæmolysis from improper storage or aging. Severe hæmolytic reactions have a mortality of not less than 25%, mainly from acute tubular necrosis. The administration of incompatible blood is usually due, not to an error in grouping or cross-matching, but to giving the wrong bottle of blood through failure to check the label. If we give blood of the same A B O group as the patient, and only Rh-negative blood to Rh-negative patients, and carry out careful cross-matching of donor's cells against patient's serum for every bottle of blood, hæmolytic reactions will be very rare and usually mild.

Hæmolysis of blood before transfusion occurs with aging or improper storage. Blood should not be used if it has been stored, even under ideal conditions, for fourteen days or more. It is essential that hospitals which undertake transfusions should provide refrigerators regulated to a temperature between 6° and 8° C., and specially reserved for the storage of blood. It is dangerous to store blood in ward refrigerators, which are used for the storage of food, and which, owing to frequent opening and shutting, are subject to wide variations in temperature. Blood which has been frozen or heated is hæmolysed and dangerous to patients. If blood has to be warmed before transfusion—as, for example, in exchange transfusion in infants—it must be warmed under careful control and never to a temperature greater than 37° C.

Packed cells cannot be stored, and must be used within twelve hours of preparation.

General anæsthesia masks the classical signs of the hæmolytic reaction. The only untoward signs may be a drop in blood pressure, duskiness, and increased bleeding in the operative field. For this reason very special care is necessary to see that the patient is being given the correct bottle of blood when a transfusion is being given during an operation.

The Transmission of Disease by Transfusion.

Under very rare conditions blood collected with scrupulous care may be infected by certain bacteria in the deeper layers of the donor's skin, which are capable of multiplying at blood bank temperature. The danger is increased by storing the blood.

Syphilis is excluded by routine serological testing of donors. Storage of blood for seventy-two hours will kill any contained *Treponema pallidum*.

Malaria is excluded by avoiding all donors who have a history of malaria, or who have had suppressive treatment during the preceding twelve months. In this State there is an extremely small risk of contracting malaria from a transfusion.

The most significant disease transmitted by transfusion is homologous serum hepatitis. Lehane (1949) gives its incidence as 0·8% after the use of whole blood. There is no known way of avoiding this danger. The incubation period is forty to 130 days, the mortality rate being variously reported as 0·2% to 10% (DeGowin *et alii*, 1949).

Circulatory Overload.

Circulatory overload is more common in medical than in surgical practice. It can occur in surgical patients if transfusions are given too rapidly or are too large. The elderly patient, the patient with severe chronic anæmia and the patient with atherosclerosis or ischæmic heart disease, is particularly liable to this hazard. The risk can be lessened by using packed cells for pre-operative transfusions, by giving the transfusions slowly and with careful observation of the neck veins, and by completing the pre-operative transfusion well before operation.

Conclusions.

1. The use of blood transfusions has been of immense value in surgery in the treatment of hæmorrhage, trauma and burns, and has greatly increased the scope of surgery.

2. Blood transfusions have appreciable risks to the patients from hæmolytic reactions, circulatory overload and the transmission of homologous serum jaundice.

3. The giving of an unnecessary transfusion places the patients at avoidable risk, and wastes a commodity of great value, not only for its intrinsic usefulness to others, for whom it may be life-saving, but also for the spirit of charity and public service which actuates those who provide it.

4. Surgeons can discharge part of their great debt to the Red Cross Blood Transfusion Service by discouraging over-ordering of blood, by forbidding unnecessary transfusions, and by directing relatives of recipients to the blood bank.

Acknowledgements.

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THE USES AND ABUSES OF BLOOD TRANSFUSION.[1]

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THE main uses of blood transfusion are, first, the provision of red cells and, secondly, the restoration of plasma volume. Both of these requirements are of the greatest importance.

The actual usage of whole blood in New South Wales has been shown by the Red Cross Blood Transfusion Service to be as follows: non-traumatic surgery, 38·2%; non-surgical hæmorrhage, 23·5%; obstetrics, 18·3%; anæmias, 10·8%; traumatic surgery, 4·3%; other blood dyscrasias, 2·8%; other reasons, 2·1%.

The surgical aspects of this subject have been discussed in another paper by Dr. Kevin Fagan. It is interesting to note the comparatively small requirements for traumatic surgery.

Non-Surgical Hæmorrhage.

In general, one can state that the main indication for the transfusion of whole blood is the restoration of blood volume, when blood volume has been reduced by hæmorrhage. Blood volume may be restored by other fluids, such as physiological saline, isotonic glucose solution in distilled water, gum acacia, dextran and serum. These fluids have their particular indications, but are best used when lowered blood volume is due to causes other than hæmorrhage—for example, dehydration. Serum is passing out of favour, because of the greater incidence of hepatitis after serum transfusion as compared with that after whole blood. The use of serum from smaller pools of donors has lowered this incidence. The fact that whole blood is just as satisfactory in those cases in which serum was formerly used is restricting the use of serum to emergencies and to remote areas.

When actual blood loss has taken place, the only satisfactory choice is whole blood. Hæmatemesis and melæna are commonly associated with much blood loss, and it is one's impression that patients with this condition are not given enough blood. Obvious external blood loss should be made good with an equal amount of blood, and one must realize that quiet bleeding may be going on without external loss. The classical indications for transfusion mentioned in text-books—namely, a rising pulse rate and a fall in the blood pressure and hæmoglobin level—may be entirely absent. There are three stages in compensation for hæmorrhage. First, there is a stage in which the pulse rate and blood pressure may be completely normal. Some subjects may lose up to one litre or more without any disturbance of the pulse or blood pressure, and may yet be in urgent need of transfusion. In the next stage sufficient blood loss has occurred to lower the cardiac output, and the patient becomes cold and clammy, with a raised pulse rate and lowered blood pressure; the urgency of transfusion is then apparent to all. Frequently, however insufficient blood is given to patients even at this stage. At any time during a hæmorrhage a patient may faint. This may be a vasovagal attack, such as may occur in nervous blood donors. In a patient with gastro-intestinal hæmorrhage, however, fainting must be regarded as a sign of serious import and as an indication for massive transfusion.

In patients who have had severe hæmorrhages there is often a third stage, in which the blood volume has been restored by mobilization of tissue fluid, but in which there is a severe degree of anæmia. These patients have a hyperdynamic circulatory state, with greatly increased cardiac output, bounding pulse and warm extremities. Transfusion of whole blood is extremely dangerous, since it overloads the heart and may cause acute pulmonary œdema. These patients should be given packed red cells instead of whole blood.

Some comment is necessary with regard to the hæmoglobin level. Just after a severe hæmorrhage the hæmoglobin value is normal, because cells and plasma have shared equally in the loss of plasma volume. The hæmoglobin level does not begin to fall until tissue fluid is mobilized to restore plasma volume. It takes about seventy-two hours for this process to be completed; therefore a continuous drop in the hæmoglobin level does not necessarily mean that bleeding is continuing, although it may well be doing so. Certainly one should not wait for a drop in hæmoglobin level before ordering blood for a patient.

Anæmia.

Nearly 11% of transfusions are given for anæmia. The first question to be decided is whether or not the patient truly has anæmia. Not infrequently patients with about 11 grammes *per centum* of hæmoglobin are given transfusions for anæmia, whereas persons with 12·4 grammes of hæmoglobin *per centum* are frequently accepted by the Red Cross as blood donors. Transfusion of mildly anæmic persons is unjustified except prior to surgery, and blood should not be used for non-medical purposes such as clearing a hospital bed. In iron-deficiency anæmias transfusion is seldom justified, except when hæmorrhage is responsible. In these anæmias the response to iron is so good that transfusion has nothing to offer in preference to more rational therapy. The same applies to pernicious anæmia, in which transfusion is meddlesome and interferes with one's investigations. Furthermore, transfusion of whole blood in this condition is often dangerous, because of the hyperdynamic circulatory state and the degeneration of the myocardium that are present in severe cases.

The main types of anæmia in which transfusion is of value are the aplastic and hæmolytic anæmias, and anæmias secondary to other diseases. In aplastic anæmia transfusions provide a substitute for normal marrow function. The life of the transfused red cell approximates to that of the normal—that is, about 100 days. It is therefore possible to give transfusions at fairly infrequent intervals, usually two or three months. In some hæmolytic anæmias, on the other hand, the life of transfused red cells may be shortened by destructive mechanisms in the recipient, so that frequently repeated transfusions are often necessary. In these individuals antibodies frequently develop towards the less well-known blood groups in transfused blood, so that cross-matching becomes difficult. Furthermore, the iron derived from the destroyed red cells is not excreted, but is stored in the tissues, and cases of transfusion hæmosiderosis are reported from time to time.

Other indications for transfusion are the anæmias of chronic nephritis, chronic sepsis, leuchæmia, and Hodgkin's

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on June 30, 1955.

disease. In the treatment of anæmia transfusion of packed red cells is far preferable to that of whole blood, since the plasma volume is normal in these conditions and the transfusion of plasma is unnecessary.

Some of the other blood dyscrasias require some comment. Leucopenic states such as agranulocytosis are treated with blood transfusions so as to relieve the anæmia that accompanies them. However, transfused white cells are non-viable, and it is useless to attempt to raise the white-cell count by means of transfusions. The same applies to thrombocytopenia. Platelets disintegrate rapidly on glass surfaces, and do not survive transfusion when given in the usual way. It is possible to transfuse viable platelets when blood is collected in silicone-lined apparatus. However, it has now been shown that destructive mechanisms for platelets exist in the plasma of many patients with thrombocytopenic purpura, and that, furthermore, platelet groups analogous to blood groups exist, so that group incompatibility is likely. Transfusion of platelets does not appear practicable or worth the trouble that it would entail.

Hæmophilia is not infrequently the cause of serious prolonged hæmorrhages that may require the provision of many bottles of blood. Operations on hæmophiliacs are fraught with danger, and repeated massive transfusions of fresh blood are often needed for these patients. Anti-hæmophilic factor is present in the plasma in association with fibrinogen fraction, which is now being prepared by the Commonwealth Serum Laboratories. Intravenous injection of this fibrinogen fraction, containing antihæmophilic factor as a contaminant, is good treatment for hæmorrhage due to hæmophilia, and may control it. It is of interest that, although only minute quantities of antihæmophilic factor are needed to restore the coagulation time of hæmophilic blood to normal *in vitro*, extremely large amounts of fresh blood are often required to stop hæmorrhage in hæmophilia. The reason for this is not clear.

Another interesting condition, fortunately a very uncommon one, is fibrinolysis in association with obstetrical accidental hæmorrhage or thoracic surgery. Fibrinolytic enzymes cause the disappearance of the patient's fibrinogen, with the result that exsanguinating hæmorrhages may occur. Massive transfusions of whole blood are urgently required. Fibrinogen fraction may be given if it is available.

It is now time to discuss some of the dangers of blood transfusion and their prevention. I am indebted to memoranda prepared for the National Blood Transfusion Committee of the Red Cross Society for much of the information on this subject.

The first problem is that of infected blood. Blood is an admirable culture medium for organisms, and fatalities from transfusion of infected blood have been recorded in many countries. Infection may be from bacteriæmia in the donor or from improperly sterilized apparatus; but it is more commonly due to contamination during collection or after collection—caused, for example, by inserting needles through the bung. Most of the organisms that contaminate blood do not grow well at low temperatures. In nearly every instance in which patients have been given contaminated blood it has been found that the blood has been removed from the refrigerator and allowed to remain for some hours at room temperature. This has permitted rapid multiplication of organisms which were previously dormant. It follows that blood should be given to the patient as soon as possible. If the transfusion is not commenced within sixty minutes of removal of blood from the refrigerator, the blood should be labelled as unsafe for patients. Similarly, if it is ever necessary to insert a needle through the bung, the blood should be given within an hour or be labelled as unsafe.

With regard to refrigeration, it is necessary to mention physical changes in red cells produced by extremes of heat or cold. If blood is stored next to the cooling element in a refrigerator, it may freeze. Blood which has been frozen should never be used.

Blood should never be heated prior to transfusion. It is safer and better to transfuse cold blood than to risk heating it and thereby causing hæmolysis.

Another important question is the length of storage. Packed red cells should be used within twelve hours of preparation and should be labelled as unfit for use after that time. With regard to whole blood, it is safe and useful for much longer. It is a routine procedure for whole blood to be withdrawn from service if it is not used within a week of collection, although a longer period of storage would be fairly safe. However, sometimes a bottle of blood may be left in a refrigerator for some weeks and then inadvertently given to a patient. The red cells and many of the plasma proteins would be non-viable, and the patient would be endangered.

The next danger to be discussed is that of giving incompatible blood. In every instance the blood administered should be of the same group as that of the patient. The practice of giving group O blood to all recipients is undesirable and negligent, the reason being that a proportion of group O donors have strong agglutinins that may hæmolyse the red cells of group A or B recipients.

Rh-negative women under middle age should not be given Rh-positive blood. Except in cases of extreme urgency, a cross-matching test should always be performed. The usual test is performed by mixing a drop of the donor's red cells with the patient's serum and looking for agglutination. This test detects incompatibilities of the A B O system, but not of the other systems, such as the Rh system. It is desirable to test also for incomplete antibodies by means of the individual Coombs test or the polyvinylpyrrolidone test published by the Red Cross Society. Cross-matching should be done by a pathologist or properly supervised technician, when possible. If their services are unavailable, the practitioner performing the tests must be well versed in scientific knowledge of the blood groups, and must be thoroughly familiar with these procedures.

I shall not discuss pyrogenic or allergic reactions, as their prevention is outside the sphere of this address. The last and perhaps the most important subject to be discussed is that of the human element, which is responsible for most transfusion disasters. It is possible for names of patients to be confused, so that blood from the wrong patient may be grouped and cross-matched. Furthermore, the results of the cross-matching may not be accurately transmitted from the laboratory to the medical officer supervising the transfusion. Finally, the greatest care must be taken that the patient gets the right bottle of blood. Blood should be carefully labelled and accurate records should be kept. Nurses should not be made to accept the responsibility of changing bottles of blood. Everybody concerned with a transfusion should be almost obsessional in their care in preventing the wrong bottle of blood from being given to their patients, particularly since in unconscious patients the symptoms of incompatibility will not be present. The infrequency of serious mistakes of this kind is indicative of the highly developed sense of responsibility of our hospitals and their staff.

Conclusion.

It is impossible to end a talk of this kind without paying tribute to the generosity and unselfishness of blood donors. It is through their efforts that this life-saving material is provided, free of cost, to our hospitals. In addition to the generous citizens who provide their blood, we feel deeply grateful to the Red Cross Society for their careful and painstaking work in collecting, typing and distributing blood, for testing its sterility, and for countless other services. We are fortunate in this State to have an organization such as the Red Cross, and we must regard its activities as community service of the highest order. We have the responsibility of seeing that blood is used wisely, that it is given in adequate amounts when it is needed, that it is not wasted, and that we do not harm our patients through incautious use of blood.

One feels that blood transfusion should have a promizent place in the medical curriculum. New graduates would thereby become acquainted with the proper indications for the use of blood, and would learn to avoid the risks and dangers of transfusion, so that it may remain the safe and beneficial procedure that the donors of blood would wish it to be.

Acknowledgements.

I am greatly indebted to Dr. R. J. Walsh and to the New South Wales Division of the Red Cross Society for advice and for allowing the use of memoranda prepared by the National Blood Transfusion Committee.

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RADIATION PROTECTION OF THE GERM PLASM IN DIAGNOSIS.

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FREQUENTLY in radiodiagnosis the gonads are irradiated for no other reason than that they lie in the field being examined, although they bear absolutely no diagnostic relation to the procedure undertaken. An attempt is made here to evaluate the sequelæ of this unnecessary exposure to a harmful influence and the dose received by the testis in certain examinations has been determined. The testis was selected as it is a superficial organ and therefore more susceptible to damage than the ovary.

As long ago as 1927 Muller demonstrated that the changes which are brought about in the cell nucleus by radiation result in heritable changes in the organism. These changes brought about by a biochemical process following the passage of the ionizing quanta are referred to as radio-induced mutations, and consist mainly of two types—the so-called structural changes and point mutations. The former are visible microscopically and may be detected after irradiation. The actual chromosome thread is fragmented and on reunion of the ends the linear arrangement of the portions of the thread may be reversed, heritable characteristics being thus produced. In point, or gene, mutations no abnormality is visible microscopically and the changes can be assessed only by a deviation from normal in later generations. Both types of mutation occur spontaneously and the effect of radiation is to increase this rate. There is no threshold below which the mutation rate is not changed, and the effect is cumulative. Other changes are also produced in the cell; these hinder its ability to undergo subsequent division and manifest themselves as impaired fertility and sterility.

Sequelæ of Irradiation.

If it is agreed that most mutations are undesirable, any increase in the mutation rate is inadvisable. Since most mutations are recessive, an increased rate will not be apparent for many generations, and the patients now in hospital for genetic reasons may be suffering because of mutations induced many generations ago. Whereas in Nature equilibrium is maintained by the balance of mutation and selection, in man a mutated recessive gene must float in the population until it appears in a homozygous state as a gross abnormality and is eliminated owing to the failure of the individual to breed. The greater the mutation rate, the greater will be the number of genes to be eliminated, and hence the greater the proportion of the population hospitalized for genetic reasons.

It is possible to calculate the dose necessary to double a given mutation rate (Evans, Howard), but until the latter can be determined accurately the exact relation between dose and genetic damage must be largely speculative. Evans showed that if the whole population up to the end of the child-bearing age received a dose of 140*r* to the gonads per generation the number of congenital abnormalities appearing after many generations would be no more than doubled. Howard points out that if the natural rate is only one-tenth of the value used in this calculation (a figure thought by many geneticists to be nearly correct) the required dose is only 14*r*, or 140*r* to only 10% of the population.

Over a range of some twenty different radio-diagnostic examinations the mean gonad dose was found by Stanford to vary from 0·2*mr* during chest radiography of males up to 27*r* during hysterosalpingography. Osborn then made use of these results to estimate a mean gonad dose per head of population, assuming the mean age of parentage to be thirty. For all diagnostic procedures, and taking into account such things as mass chest surveys and increased pædiatric dosage, the dose for the thirty-year period over the whole population was approximately 0·2*r*. This would be equivalent to increasing the spontaneous rate by about 1·5%. If it was assumed that natural background radiation, that is, natural radioactivity and cosmic rays (variously estimated at 1·5 to 3·0*r* for the thirty-year period) alone accounted for spontaneous mutation, the increase due to diagnostic procedures would be in the vicinity of 5% to 10%. However, over the next generation the widening application of radioactive materials both in medicine and industry and the increasing number of people voluntarily and involuntarily exposed to them may render more cogent in the field of radiodiagnosis the recommendation of the International Commission on Radiation Protection that "every effort be made to reduce exposures of all types of ionizing radiation to the lowest possible level". Radiation protection will resolve essentially into a new kind of public health problem. It can be expected then that there will be a tendency to obtain protection by legislation. Medicine should therefore take the lead in instituting protective measures and in so doing should first have its own house in order.

Recent experiments (Carter *et alii*) concerning the effect of radiation upon fertility have shown that more important than the dose is the time over which exposure is continued. Thus 200*r* given as a whole body dose in six weeks had no effect on fertility, while if spread over twenty-five weeks it had a marked sterilizing effect. Further work in Edinburgh, which will take some years to complete, is proceeding following the finding that a dose of 40*r* probably caused the same effect.

Radiation of the gonads is thus known to be harmful and its effect cumulative. The risk run in some procedures, including those for which measurements are quoted below, would seem to be appreciable, and, further, this risk undertaken is quite unnecessary and wholly avoidable. We feel that the risk should be acknowledged and a gesture made for the time being at least in affording protection in these obvious cases of exposure whilst awaiting the decisions of further research. By modifying such techniques in which radiation to the gonads is excessive the total dose to the population could be significantly lowered.

Dosage.

A Victoreen dosemeter was used to measure the dosage rate from two typical X-ray plants used at the Royal Alexandra Hospital for Children, Sydney, with a view to estimating the dose received by the testes during examination for congenital dislocation of the hip, Perthes's disease, and tuberculous hip disease.

Each examination involves an antero-posterior and a lateral view, and is repeated twenty to thirty times during a period of two to three years. The physical factors used are: 55 kilovolts peak, 40 inches film distance, and 50 or 75 milliampère seconds, according to age and size. The estimated dose received by the testes (1·0 centimetre depth

dose) for various filters is shown in Table I for an exposure of 75 milliampère seconds. Many plants are still used without additional filtration, and even with the addition of 2·0 millimetres of aluminium the dose received by the testis is still too high when it is not necessary. It may be reduced to negligible proportions (less than one-thousandth) by means of a lead box made from 0·5 millimetre lead. The one being used at present is in the form of an elliptical lead shield kept in place by elastic straps.

Measurements made during barium enema examination and the taking of an excretion pyelogram on adults indicate that, with correct coning and the use of 2·0 millimetres of aluminium added filter, the dose to the testes can reach 1·5*r*. When it is considered that in children the gonads are not as a rule restricted from the diagnostic field, these and other procedures may also be suspect.

TABLE I.

Plant.	Filter.	Dose. (20 to 30 Examinations.)
Maxygraph ..	Inherent only.	30–45*r*
Maxygraph ..	Inherent+1 mm. Al.	12–18*r*
Maxygraph ..	Inherent+2 mm. Al.	8–12*r*
Stanford ..	Inherent+1 mm. Al.	18–27*r*

Conclusions and Recommendations.

Because of the lack of quantitative knowledge of the relation of radiation to human genetics it is difficult to know how much radiation is dangerous. It is unfortunate if we adopt a casual approach to a distant problem, as the genetic effect is a real one, radiation mutagenesis lacks a threshold and all radiation received by the gonads entails some risk to later generations. With expansion in the use of radioactive materials the genetic "load" will be increased. It should, therefore, be the aim of all engaged in the use of radiation to keep the exposure of the gonads to as low a level as possible. Attention is drawn to the unnecessary exposure of the germ plasm in some diagnostic procedures. Particular reference is made to children undergoing serial examinations for diseases of the hips. The dose received by the gonads can be significantly lowered by restriction of the field to diagnostic areas, proper coning, additional filtration and shielding.

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It is a pleasure to record discussions of these problems with Dr. J. M. Rendel, Officer-in-Charge, Commonwealth Scientific and Industrial Research Organization, Animal Genetics Division, at the University of Sydney.

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A SHORTER METHOD FOR DETERMINING THE LATENT IRON-BINDING CAPACITY OF SERUM.

By I. KALDOR.[1]

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IRON present in blood serum is bound to a specific protein (Schade and Caroline, 1946) which has been given various names—transferrin (Holmberg and Laurell, 1947), iron-binding protein (Rath and Finch, 1949), siderophillin (Schade, Reinhardt and Levy, 1949), and β_1-metal combining globulin (Surgenor, Koechlin and Strong, 1949). As this protein is normally present in excess of the amount required to carry the iron of the serum, it is possible to measure the amount of unsaturated protein in terms of the iron which could be bound. This value is called the latent iron-binding capacity. When it is considered in conjunction with the serum iron value, the latent iron-binding capacity is a valuable aid in the diagnosis of certain blood dyscrasias and disorders of iron metabolism, such as iron-deficiency anæmia, anæmia of infection and hæmochromatosis.

Various methods have been devised for estimating the iron-binding capacity of serum. The method of Schade and Caroline (1946) is based on a microbiological principle, whilst that of Laurell (1947) relies on certain physico-chemical properties of transferrin-bound iron. A more recent method (Reinstein, Bethard and McCarthy, 1953) utilizes radio-iron for estimating iron-binding capacity. None of these methods is suitable for routine laboratory use.

The method described by Rath and Finch (1949) and by Cartwright and Wintrobe (1949) has been most frequently used in the past. This method, which will be termed the "standard method" in this paper, is based on the fact that a red colour develops when iron is added to and unites with unsaturated iron-binding protein. The standard method is to add iron in small increments to serum, and after each addition to measure the colour developed in a sensitive photoelectric colorimeter. Maximum colour is developed, and the colorimeter reading becomes constant when the protein is saturated with iron. The amount of iron required to produce this saturation represents the latent iron-binding capacity of the serum.

It is the purpose of this paper to describe a shorter and quicker method which can be used in any laboratory with a sensitive colorimeter. The method was first suggested by Laurell (1947), and later described by Ventura (1952). Iron in excess of the amount which could be bound by the protein is added to a measured quantity of serum. The difference in colorimeter readings before and after addition of the iron is used as a measure of the latent iron-binding capacity. However, it is necessary at the outset to calibrate the instrument by testing several different sera by the standard method. Details of the method and of the calibration of the colorimeter will be described.

Materials.

Serum.

Venous blood is collected in the morning from fasting subjects. It is allowed to clot and then centrifuged. The supernatant serum is best used for the latent iron-binding capacity test as soon as possible after collection, and always within twenty-four hours. If it is necessary to leave the sample overnight, it should be stored in the refrigerator (6° C.). An amount of 1·5 millilitres of serum diluted with an equal volume of saline is required for a single test. This dilution is prepared in the colorimeter

[1] This work was undertaken during tenure of a National Health and Medical Research Council Fellowship.

cuvette immediately before the test is carried out. It is important that the temperature of the diluted serum aliquot and that of the cuvette be the same as the ambient temperature. Turbidity, hæmoglobin from hæmolysis or high pigment concentration renders serum unsuitable, because all these tend to mask colour changes during the test.

Standard Iron Solutions.

Standard iron solutions of two different strengths are required, solution A for the standard procedure and solution B for the shorter method.

For the preparation of solution A, 0·0657 gramme of ferrous ammonium sulphate is dissolved in 0·5 millilitre of normal acetic acid in a 250 millilitre volumetric flask, and made up to volume with distilled water. The addition of 0·02 millilitre of this solution to 1·5 millilitres of serum corresponds to 50 microgrammes of iron per 100 millilitres of serum.

Solution B is prepared as follows: 0·1578 gramme of ferrous ammonium sulphate is dissolved in 0·5 millilitre of normal acetic acid in a 100 millimetre volumetric flask and made up to volume with distilled water. The addition of 0·05 millilitre of this solution to 1·5 millilitres of serum corresponds to 750 microgrammes of iron per 100 millilitres of serum.

Physiological Saline.

For the preparation of physiological saline 0·9 gramme of sodium chloride is dissolved in 100 millilitres of distilled water.

Distilled Water.

Distilled water used for making up solutions, or for the final rinsing of glassware is redistilled in an all-glass still.

Cleansing of Glassware.

All glassware, including the syringe used for collecting blood, is cleansed in turn with warm detergent solution, tap water, distilled water, approximately 0·5 normal solution of hydrochloric acid, and double-distilled water.

Photoelectric Colorimeter.

The photoelectric colorimeter used has been described in detail elsewhere (Kaldor, 1953*a*), but the following features relevant to the present work should be noted. The instrument is equipped with a single photocell, and has a light source of variable intensity controlled by two potentiometers. The photocell is connected through a switch to a direct reading Cambridge spot galvanometer of 450 ohm internal resistance, with a reading scale calibrated in 100 linear units. An Ilford "EEL 624" light filter with a transmission peak at 520 millimicrons is used. The cuvettes have an optical path of 13 millimetres and require a minimum of three millilitres of liquid.

The Standard Method.

Apart from slight modifications, the standard method is essentially the same as that described by Rath and Finch (1949). Serum (1·5 millilitres) and saline (1·5 millilitres) are pipetted into a colorimeter cuvette and mixed with a Pasteur pipette. The percentage light transmission is then determined in the colorimeter against saline as the blank solution. Once this "baseline value" has been determined, 0·02 millilitre of the standard iron solution A is added from a microburette. The contents of the cuvette are mixed with the Pasteur pipette and the percentage light transmission is determined after an interval of ten minutes. If any change from the baseline value occurs, further 0·02 millilitre volumes of solution A are added, and the percentage transmission values are determined five minutes after each addition. The additions are continued until the transmission value remains constant after two successive additions of the iron solution. The percentage light transmission values obtained in this manner are converted into density values by the following formula:

$$\text{Density} = 2 - \log \text{percentage transmission.}$$

The baseline density value is subtracted from all density values, and the resulting figures are termed "reduced densities". These values are plotted on graph paper against the amounts of iron added. Two straight lines are obtained, and their point of intersection is projected to the abscissa. This indicates the amount of iron required to saturate the latent iron-binding capacity. A typical protocol is shown in Figure I.

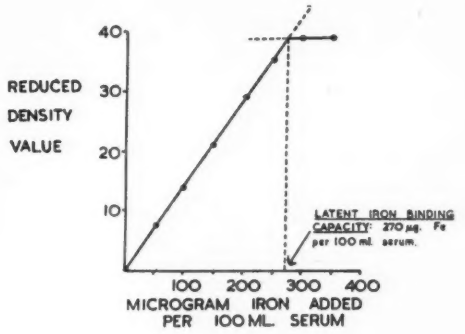

FIGURE I.

Typical protocol of a latent iron-binding capacity test by the standard method (see Table III).

The Shorter Method.

The shorter method is based on the fact that the slope of the curve constructed by plotting reduced densities against amounts of iron added (see above) does not vary greatly with different sera. The mean slope of six determinations by the standard method provides a satisfactory calibration curve. From such a curve the latent iron-binding capacity of any serum may be obtained, once the difference between its density before and after saturation has been determined.

Construction of the Calibration Curve.

The latent iron-binding capacity is determined on six sera by the standard method described above. The reduced density values after each addition of iron are obtained and plotted as shown earlier. All those values obtained on or after saturation are then excluded, and the mean values of the remainder are calculated for each increment of iron. This is shown in Table I. The calibration curve is drawn from the mean values as shown in Figure II.

TABLE I.

Construction of Calibration Curve for the Shorter Method.[1]

Series Number.	Reduced Density Values Obtained after Addition of the Amounts of Iron Shown. (Microgrammes of Iron per 100 Millilitres of Serum.)							
	0	50	100	150	200	250	300	350
1	0	12	18[2]	18[2]				
2	0	8	12	20	24[2]	23[2]		
3	0	7	14	19	25[2]	23[2]		
4	0	7	14	20	30[2]	28[2]		
5	0	6	13	19	27	33	39[2]	39[2]
6	0	7	15	22	30	35	37[2]	37[2]
Total	0	47	68	100	57	68		
Mean	0	7·8	13·6	20·0	28·5	34·0		

[1] Only the computed reduced density values are shown in this table. For explanation, see text.

[2] These figures are excluded from the calculation, as the serum has been saturated with iron.

Technique of the Test.

Serum (1·5 millilitres) and saline (1·5 millilitres) are pipetted into a colorimeter cuvette and mixed with a Pasteur pipette as in the standard method. The percentage light transmission is then determined against saline as blank. It is again determined ten minutes after the addition and mixing of 0·05 millilitre of the standard iron solution B. This corresponds to the addition of 750 microgrammes of iron to 100 millilitres of serum, an amount which is in excess of the latent iron-binding capacity of normal or abnormal sera. The reduced density of the second reading is computed as in the standard method. The latent iron-binding capacity corresponding to this value is then obtained from the standard curve.

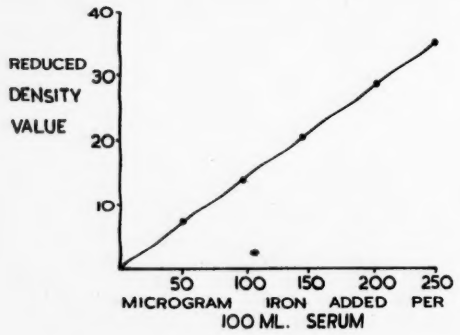

FIGURE II.

Calibration curve for the shorter method by the use of values obtained from six sera.

Comparison of the Two Methods.

The latent iron-binding capacity was determined by both methods on 14 sera, some of which were obtained from blood donors, others from patients with various clinical conditions. The calibration curve for the shorter method was constructed from data obtained during the performance of the standard tests. The results are shown in Table II. It is to be noted that the mean values are almost identical with the two methods, but that there is a difference of up to 80 microgrammes in individual instances. It is probable that the error of the standard method is large, but there is no reason to believe that the error of the shorter method is much larger.

TABLE II.

Comparison of Results Obtained with the Standard Method and with the Shorter Method on Fourteen Sera.

Serum Number.	Latent Iron Binding Capacity. (Microgrammes per 100 Millilitres of Serum.)		
	Standard Method.	Shorter Method.	Difference.
1	320	390	+70
2	190	180	−10
3	190	190	0
4	330	330	0
5	300	280	−20
6	220	250	+30
7	150	170	+20
8	200	150	−50
9	210	230	+20
10	220	220	0
11	300	250	−50
12	260	260	0
13	300	320	+20
14	370	410	+40
Total ..	3560	3630	+70
Mean ..	254	259	+ 5

Discussion.

The standard method for measuring the latent iron-binding capacity is tedious and time-consuming, and has not been widely used. The shorter method should render the test more suitable for routine laboratories. Although it may be slightly less accurate than the standard method, it is probably adequate for the diagnosis of clinical conditions. It must be admitted that sera containing large amounts of pigments, such as hæmoglobin or bilirubin, or those which are turbid, cannot be tested by the shorter method without large error.

TABLE III.

Protocol for Figure I.

Amounts of Iron Added. (Microgrammes per 100 Millilitres of Serum.)	Percentage Transmission.	Log Percentage Transmission.	Density (2 − log Percentage Transmission.)	Reduced Density ×1000.
0	70·2	1·846	0·154	0
50	68·9	1·838	0·162	8
100	67·9	1·832	0·168	14
150	66·8	1·825	0·175	21
200	65·6	1·817	0·183	29
250	64·7	1·811	0·189	35
300	64·2	1·806	0·193	39
350	64·2	1·806	0·193	39

Normal commercial photoelectric colorimeters are sufficiently sensitive for measuring the latent iron-binding capacity of serum. However, the sensitivity of every instrument must first be tested. A sample of normal serum should be tested by the standard method and the reduced density values plotted as in Figure I. The instrument is suitable if these values are separated by intervals of the same order as those shown in Figure I and Table I.

Summary.

A short method is described for determining the latent iron-binding capacity of serum. The method, which was first presented by Ventura (1952), involves measurement of the light transmission of a diluted serum sample before and after saturation of its iron-binding capacity, and requires the calibration of the photoelectric instrument used. A simple procedure is described for this calibration.

Acknowledgement.

The writer wishes to acknowledge the technical assistance of Miss Marjorie Powell.

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FURTHER EXPERIENCES WITH "MEGIMIDE"—A BARBITURATE ANTAGONIST.

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IN a previous paper (Shulman, Shaw, Cass and Whyte, 1955), the clinical use of β,β methyl ethyl glutarimide ("Megimide") and of 2-4 diamino 5 phenyl thiazole (D.A.P.T., "Daptazole", DHA-245) in the treatment of acute barbiturate intoxication was described. Since this paper was written, at least another 56 patients have been treated, both in this country and in England (Harris, 1955; Montuschi and Wickenden, 1955). These cases, combined with further animal experiments, have given additional clinical and pharmacological information. This paper will deal with both these aspects, but particularly the latter.

The details of treatment set out in the initial publication have not been altered. The principle consists in the slow administration of the two drugs into an intravenous infusion until a "safe state" is reached. No attempt is made to waken the patient, as this cannot readily be done without the risk of overdosage.

The results obtained in the later cases confirm those obtained previously.

1. The patients who respond most readily to treatment are those by whom 20 to 30 grains of a medium-acting barbiturate have been ingested and whose coma has not persisted for more than twelve hours. These subjects will reach a "safe state" in about one hour, and in another five hours will be obeying commands and making a few purposeful movements. Recovery from this stage is uneventful.

2. When a larger dose has been ingested or the intoxication is due to a long-acting barbiturate, as much as 1·0 gramme of "Megimide" and 0·3 gramme of D.A.P.T. may be required. Although some of these patients may be brought to a "safe state", regression is likely to occur within about eight hours and one or more further treatments will be necessary.

3. Signs of overdosage are vomiting followed by slight flickers of the fingers or fasciculation of the jaw muscles. Several patients have received excessive amounts of "Megimide", but after sedation with paraldehyde have made uneventful recoveries.

4. The first results of administration are an elevation of the blood pressure and an increase in the rate and depth of respiration. These are followed by a return of reflexes, especially the plantar withdrawal, and finally by groaning and slight voluntary movements. This is the "safe state" at which treatment is stopped.

5. D.A.P.T. is not necessary in the treatment of mild barbiturate poisoning, but it is a valuable adjunct in the treatment of severe poisoning. It increases the depth of respiration and lessens the possibility of excessive treatment with "Megimide"; its use is recommended.

The advantages of this method of treatment of barbiturate intoxication are as follows: (i) It removes the necessity for prolonged endotracheal intubation. (ii) It minimizes both the immediate risk to the patient's life and the remote risk which may follow the onset of complications often accompanying prolonged barbiturate coma. (iii) It is valuable from the viewpoint of hospital economy and the relief it affords from the burden of prolonged and strict nursing. On the average there may be a saving of as much as three days in hospital per patient. (iv) It may serve to distinguish barbiturate from other types of poisoning or differentiate the coma from other causes. If after about 0·2 gramme of "Megimide" has been administered there is no change in the patient's condition but signs of "Megimide" overdosage are evident, then one can look for other causes to account for the coma—for example, cerebro-vascular accident. If 1·0 gramme of "Megimide" has been administered without signs of toxicity (or improvement), another poisoning agent should be suspected. This has been noticed in two cases in which chlorpromazine has been involved.

No good purpose would be served by a summary of all the cases of barbiturate poisoning treated since the original publication. However, the following two reports do illustrate the results obtained in a mild and in a severe case of poisoning.

Reports of Cases.

CASE I.—A female patient, aged forty-five years, weighing about seven stone and emaciated, had taken 30 grains of "Amylobarbital" about eight hours previously. On her admission to hospital routine supportive treatment was given. Her systolic blood pressure was 65 millimetres of mercury, her pulse rate was 50 per minute, respirations numbered eight per minute and were barely discernible. Areflexia was present. Treatment with "Megimide" and D.A.P.T. was commenced, and one hour later 0·5 gramme and 0·2 gramme respectively had been given. Her systolic blood pressure was then 115 millimetres of mercury, her pulse rate was 70 per minute, and her respirations numbered 14 per minute and were deeper. All reflexes had returned, and the patient was groaning and making slight voluntary movements. Regression did not occur. The patient made an uneventful recovery.

CASE II.—A male patient, aged forty years, had taken 113 grains of "Pentobarbital" about five hours earlier. He was admitted to hospital and supportive treatment was given. His systolic blood pressure was 120 millimetres of mercury, his pulse rate was 100 per minute, and his respirations numbered 30 per minute and were shallow. The patient was deeply comatose and areflexic. Treatment was commenced, and ninety minutes later, after 0·3 gramme of "Megimide" had been given, the patient aroused himself and pulled out the intravenous needle. His blood pressure was 130 millimetres of mercury, systolic, and 80 millimetres, diastolic; his pulse rate was 100 per minute; his respirations numbered 24 per minute and were deep. All reflexes returned and the patient responded to stimuli. Subsequently the patient regressed, although the blood pressure, pulse and respirations remained almost as before. The patient was then given "Megimide" (0·1 gramme) and D.A.P.T. (60 milligrammes) over half an hour. The respirations increased in depth but not in rate. The patient responded to simple commands and tried to sit up. A slight regression was again corrected with "Megimide" (60 milligrammes), and the patient made an uneventful recovery.

Discussion.

There are at present two schools of thought regarding the treatment of acute barbiturate poisoning, which agree only in so far as good management is the first essential. The first school is led by Nilsson (1950), who regards the problem as "an anæsthesia which is drawn out to last for days instead of hours". The other school, of Koppanyi (1954), regards the problem as one of pharmacology. The principle of antagonism is well established in general pharmacology. If one can obtain drugs which will completely abolish the action of, say, histamine, why should one not try to obtain the same negation of effect for the barbiturates?

The concept of Nilsson implies that there is no lethal dose of barbiturate. The concept of a lethal dose for all drugs is too well established in pharmacology to need comment. It is the aim of experimental pharmacologists to obtain an antagonist for every drug used in medicine —for example, antihistaminics, adrenergic blockers, decurarizing agents, atropine, and N-allyl-normorphine or 2·4 diamino 5 phenyl thiazole (Shaw and Shulman, 1955).

Koppanyi and his followers have investigated the possibility of obtaining antagonists to the barbiturates. At first strychnine was tried and later picrotoxin and pentylenetetrazole. It is not the purpose of this paper to discuss the use of these compounds, as we believe "Megimide" to be of greater usefulness. Nevertheless, the results obtained with those drugs cannot be ignored.

Nilsson states that "it cannot be considered physiological to stimulate a cerebrum, depressed by barbiturate poisoning, so intensively that the organism is permanently poised on the border of a state of convulsion". Physiology is an inductive science, and there are no *a priori* principles by which one can consider a process to be "physiological" or otherwise.

Analeptics are commonly taken to mean drugs having a stimulating and strengthening effect. Centrally acting analeptics have been widely employed in recent decades in all forms of circulatory collapse, both peripheral and central. In many cases the rationale for their use stems back to the day when it was thought indecent to die without at least one injection of camphor. I would agree with Nilsson in condemning the non-specific use of analeptics. One cannot restore the metabolism of a damaged cell by the introduction of a foreign substance. If a case is to be made for the use of drugs in the treatment of barbiturate poisoning, it must rest on experimental antagonism and not on theoretical analepticism.

It must be conceded from the point of view of experimental pharmacology that the usual analeptics have shown promise, but can under no circumstances be considered to be ideal antagonists. From the clinical point of view their success has been qualified. This is not entirely the fault of the drug, but is due to the fact that the compounds have often been asked to do impossible tasks. If lack of oxygen or excess carbon dioxide has damaged cerebral cells, then no drug will rejuvenate this tissue.

Perhaps the point which has been most stressed by the opponents of the use of analeptics is the statement that these drugs provoke an anoxic cell to use more oxygen. Why this in itself should result in further harm to the cell again can be explained only on a "rational" basis; so far it has not been explained on an experimental one.

There are two papers which provide experimental evidence to show that analeptics increase the oxygen consumption of the cells of the central nervous system. The paper by Davies and McCulloch (1944) lacks any quantitative data. One is not told what doses of drugs were used and what were the effects of non-convulsant doses; the paper is no more than a note on how an oxygen electrode may be used. A paper mentioned in their bibliography, purporting to give a detailed account of the results obtained, has never appeared. The paper by Schmidt (1945) is more definite. This author measured the arteriovenous oxygen difference of blood flowing through the head. In each case the drug was given in such a dosage as to produce convulsions. This resulted in an increased oxygen uptake by the brain.

Electrical convulsions produce profound biochemical changes (see review by Richter, 1952). There is, however, no evidence that analeptic drugs or electric shock at the non-convulsive level produces alterations in the metabolism. There is another way in which one can check whether analeptics bring about increased metabolism in brain cells. It is possible to set up brain slices and measure their oxygen uptake. When this was done it was found that there was no extra oxygen consumption when strychnine, amphetamine, picrotoxin or "Megimide" was added to the slices (M. Messer, personal communication). This is a more delicate experiment than the two referred to above, in which varying concentrations were used, including those one hundred times the convulsive. At the present time it seems difficult to reconcile our results obtained on tissue slices with those of Schmidt obtained on whole brain.

Richards and Koppanyi (1954) also stress that there is no convincing evidence that the use of analeptics increases the oxygen consumption of the brain beyond the supply available to the cells.

Wright (1955) states that ". . . it should be possible to use blood barbiturate levels as a criterion in assessing the therapeutic efficacy of analeptics". Presumably there should be a fall in barbiturate blood level if the analeptic is efficacious. But there is no pharmacological evidence to suggest that antagonists bring about a more rapid excretion or destruction of the offending drug. Indeed, an inversion is necessary here. The question to be answered should be: do analeptics produce a fall in barbiturate blood levels *pari passu* with an improvement in clinical condition?

As has been stated before, it is not intended to defend the use of picrotoxin and pentylenetetrazol, but to support the use of true pharmacological antagonists in the treatment of barbiturate poisoning. It has also been agreed that the analeptics up to date are not perfect antagonists. It remains to discuss the role of "Megimide" as an antagonist. Chemically there is a greater similarity of "Megimide" to barbiturates than there is to the other analeptics. The action of "Megimide" is specific. It does not affect the depressant actions of other anæsthetic agents—for example, ether, chloroform, morphine *et cetera*, "Megimide" produces a reversal of the barbiturate-induced changes in the electroencephalogram in the dog and cat (Professor W. V. Macfarlane, personal communication). This is in contrast to the work of Mousel and Essex (1941), who found that the common analeptics produced no demonstrable change in the electroencephalogram of dogs treated with "Amytal". "Megimide" will prevent death in rats which have received twice the lethal dose of "Pentobarbitone", and the antagonism is reciprocal. "Megimide" will also enable rabbits to survive a lethal dose of thiopentone. From this evidence it will be seen that "Megimide" is to be classed as a barbiturate antagonist and not as an analeptic. By this one does not mean to imply that picrotoxin, for instance, is not a mild antagonist also, as undoubtedly animal experiments would support this classification.

The benefits to be obtained by "Megimide" when compared with conservative treatment can be judged by two criteria: lessened duration of coma and lowered mortality rate. With regard to the latter, there has not been one death in a series of over 56 cases in which the history has been one of uncomplicated barbiturate poisoning. In the one fatal case reported (Shulman *et alii*, 1955) the patient had inadvertently breathed a high concentration of carbon dioxide for a period of eight hours. The series is too small to allow one to draw valid conclusions. The results which indicate that the duration of the coma is lessened are more definite. Nilsson's (1950) own figures give an average duration of over fifty-two hours, Wright's (1955) smaller series a duration of twenty-four hours. In all our cases the patient has been brought from a comatose to a less than stuporose condition in a shorter time than eight hours. In those 12 cases in which regression occurred, the patient, with one exception, never relapsed back to a deep coma. The patients who relapsed had for considerable periods of time during the forty-eight to sixty hours of their unconsciousness, intervals (after treatment) when their blood pressure, pulse and respirations were normal and they were even able to make some kind of movement. We suggest that these patients must benefit from these "lighter" periods. They would stand a better chance of recovery than a person who remains constantly comatose for about forty hours, the period of coma to be expected in the "relapsed" series, from the nature of the dose and the time that had elapsed before treatment.

Summary.

1. The results of the treatment of acute barbiturate intoxication with β,β methyl ethyl glutarimide ("Megimide") and 2-4 diamino 5 phenyl thiazole are satisfactory in the series to date.

2. The advantages of the method of resuscitation are given, of which the most prominent are the increase in blood pressure and respiratory rate and a lessening of the coma.

3. With conservative treatment the average duration of coma is fifty-two hours. In most cases treatment with "Megimide" reduces the duration of coma to eight hours.

4. Certain aspects of the pharmacology and use of analeptics and "Megimide" are discussed.

5. "Megimide" is described as a barbiturate antagonist rather than as an analeptic.

6. The common analeptics do not increase the oxygen consumption of isolated brain tissue slices.

Acknowledgements.

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Addendum.

Since this paper was written reports have been received from England of the successful treatment of 41 cases of barbiturate poisoning by the use of "Megimide". In none of these cases was there any report of untoward effects. Several of the victims had taken doses of more than 100 grains of barbiturate, and two over 270 grains. Of particular interest are the letters of C. Holten, who has treated nine cases (*Lancet*, 1955, 2: 619), and M. S. Perinpanayagam and his colleagues, who treated a child of fifteen months who had ingested 21 grains of "Tuinal" (*Brit. M. J.*, 1955, 2: 912). The experience of both authors with regard to remissions and lack of side effects has been the same as ours. Dr. Holten considers the drug not to be a central analeptic but a true antagonist.

CAN PAIN BE HYSTERICAL?

By MICHAEL KELLY,
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There is a strong propensity amongst medical writers to set up, as it were, a number of cities of refuge, to which all those symptoms may be sent which cannot satisfactorily be assigned to definite seats. . . . This style of reasoning reminds us of the Pickwick Club, in which an insult ceased to be so when it was stated that the words were used in a "Pickwickian" sense; for in medicine, pain is no pain, and suffering no suffering, in an hysterical sense. An hysterical pain is one which a patient feels, but has not; which has no existence; but which, by being thought upon, may grow until it is unbearable.—Thomas Inman (1858).

Most of the emphasis is placed on the psychology of the patient and very little on that of the doctor. The handling of the chronic sick demands a special approach and a special understanding. It requires not only a scientific appreciation of all the varying aspects of the malady but a personal and sympathetic interest in the individual afflicted with the disease.—J. W. T. Patterson. (1948).

OUR profession, which learns its medicine out of textbooks, will always be troubled with the problem of what to do with those patients who do not conform to a textbook picture. Certain patterns of symptoms which recur frequently are easily recognized and have been given the artificial status of diseases. But the symptoms of the majority of patients do not agree with any of these patterns. They may be transient, or they may remain for years at the same intensity. If they are transient the doctor thinks of them no more; or he may give the credit to his treatment. If they are chronic the patient may remain in ill health for years without getting worse.

A Compelling Symptom.

Persistent pain is the most compelling of all symptoms. It can also be the most mysterious when it occurs without organic signs to account for it. It fits into no text-book picture; as students we learned nothing about it. It is common, especially after injury, but we tend to forget each patient in turn and treat the next one as a new and separate problem. When we are confronted with these patients in practice, we have no authority to rely on; we have to learn from our own experience and fit them after a few years into a workable scheme. Even if we cannot cure them we should listen to them and be ready with our sympathy. If, however, we have come to regard these pains as unreal, any experience we gain will be wasted.

CASE I.—About twenty years ago I suffered from generalized pains which followed a mild attack of scarlet fever. For three months I could not practise medicine, and I was kept awake at night with painful stiffness of shoulders and knees. My heels were so sore that I could not walk, but crept along with bent knees. No joints swelled; a medical friend told me I was hysterical. The symptoms have never returned.

Begging the Question.

It is fashionable today to call many such pains psychogenic (O'Neill, 1955). Hart (1954) stated that 49 out of 100 cases of pain in the neck were purely functional and 22 partly so. Bourdillon (1955) states that hysterical overlay is an important contributory cause of intractable pain in the back. There are similar examples in every second or third issue of almost any medical journal. I believe that this is a vicious trend in medicine for the following reasons:

1. It begs the question by assuming as a fact something which cannot be proved—that the idea of a pain can evoke a pain.

2. It disregards the evidence of the only witness in the case—the patient.

3. It puts the blame on the patient and brings him into contempt.

4. It offends against the cardinal principle that a disease is organic unless proved otherwise.

5. It leads to slipshod methods in history-taking and examination.

6. It leads to grievous errors of diagnosis.

Some Effects of Pain.

There are few things more pathetic than a patient with unrelieved pain who wanders from doctor to doctor, to be told by each in turn that the sufferings are in his mind only. This diagnosis admits no argument and uses every word the patient utters to convict him of involuntary shamming. The patient who is worn out with pain and lack of sleep and stupefied by drugs is for that very reason accused of mental instability. If pain follows an injury it is said to be motivated, and is labelled traumatic hysteria or a compensation neurosis. Yet painful sequelæ of injuries have been studied for many years under various names—

spreading neuralgia, ascending neuritis, Sudeck's atrophy, post-traumatic dystrophy, sympathetic dystrophy. The patient's past life is minutely examined for maladjustments and psychic strains, which are inevitably found because we all have them. And the patient, who has a real physical pain like a toothache, is told to take his mind off it.

Gordon and Whitteridge (1943) have shown that pain disturbs the α rhythm of the encephalogram. But we are more concerned here with the effects of prolonged pain on the mind. Pain is an extremely personal thing which can be shared with nobody; the sufferer speaks of "my pain". Unrelieved pain makes him curl up and shun the rest of the world; he lies and envies the other patients who are not preoccupied with pain. I once observed a soldier with causalgia change in character from a normal man to a weak and emotional complainer. As the pain slowly subsided, his character strengthened again.

Anyone who has lain awake with toothache for one night should look into his own heart before he suspects psychic pain in anybody else. Any doctor who has been laid up for a few days with acute lumbago should try to imagine that such a paralysing pain has gone on for years. But some of us have an instinctive prejudice which prevents us from considering the evidence rationally. For the patient is our only witness and it is not reasonable to disbelieve him. We ought to feel ashamed to read of tricks we are expected to play in order to catch him out; the slightest inconsistency damns him to the psychalgia class. The readiness to diagnose hysteria is born of an inability (or unwillingness) to say: "I don't know." It is fashionable because it rids the doctor of responsibility and puts the blame on the patient.

Unruly Symptoms.

I know many doctors who become grieved and annoyed with patients whose pain spreads beyond the field of a nerve trunk or root—for example, a woman with extreme lumbar pain which sometimes spreads up to the mid-thoracic level (Case IV). It is characteristic of all deep pain however, that its spread is not related to the dermatomes (Lewis, 1942; Steinbrocker *et alii*, 1953; Feinstein *et alii*, 1954). Persistent pain begets more pain, and often spreading tenderness and muscular spasm (Leriche, 1939); it does not undergo adaptation (Adrian, 1926). (While injecting procaine for somatic pain I often observe unusual pain reference. Recently an injection of procaine into the upper lumbar part of the sacrospinalis caused a vivid pain in the heel. In another patient injection into the right *gluteus maximus* caused pain in the back of the left thigh.)

Grotesque postures are given special names (for example, camptocormia) and regarded as diagnostic of hysteria. Many of these postures are due to fibrositic lesions which cause reflex spasm and tenderness, and can be cured with injections of procaine.

CASE II.—Within a few weeks I examined two patients with camptocormia. Each had a pain in the back, after which he walked with his hips bent at a right angle for several weeks. Painful spasm of the *rectus abdominis* muscles prevented him from extending his hips. On careful palpation bilateral tenderness was found in each rectus one inch above its pubic attachment. When two cubic centimetres of procaine solution had been injected into each lesion, the painful spasm disappeared and the patient was able to extend his hips. Both patients were completely cured.

The majority of patients with intractable pain do not present any obvious emotional disturbance, and of the minority who do, nearly all had the pain before they became disturbed. We should try to find out how the patient became like that, and we cannot do this without taking a careful history. These pains are commonly rheumatic; a history of rheumatic symptoms will suggest this diagnosis.

CASE III.—A patient with a severe backache of six months' duration presented no signs except scoliosis and severe pain on attempting to stoop. She said that she had never had any rheumatic symptoms; but after careful questioning she remembered that her hands had been painful and swollen for three weeks two years before. The backache was cured with "Butazolidin".

CASE IV.—A woman, aged forty years, who had hurt her back, had been disabled for six months with widespread pain, tenderness and muscular spasm. She bore it all equably until she was told by three doctors in succession that she was hysterical. Her natural resentment was invoked as further evidence of hysteria. A properly taken history reveals without doubt that she had the pain for many months before she became emotional.

The pain is as real as pain from any other organic cause; but a practitioner who is interested in psychic stresses and strains may elicit a misleading history. He may even forbid any reference to physical causes or signs on the ground that it insensifies motivation.

Errors of Diagnosis.

Hysteria used to be diagnosed even more frequently than at present. Charcot (1877) wrote of it as a cause of death; and Whytt (1765) sometimes found scirrhi in the abdominal cavities of people who had died of hysteria. During the past two years I have seen the following diseases revealed at autopsy on four patients whose pains were thought to be hysterical: carcinoma of the tail of the pancreas; carcinoma of the lung with a secondary growth in the cervical part of the spine; secondary deposit from carcinoma of the breast in the thoracic part of the spine; secondary deposit from carcinoma of the prostate in the lumbar part of the spine. Many similar errors have been reported (Gillespie, 1928; Buzzard, 1929; Klotz, 1952; Robins *et alii*, 1952; Fletcher and Jacobs, 1955; Sundt, 1955). For the patient and his relatives such an illness is harder to bear when it is treated at the beginning almost as a joke. These errors would not happen if students were taught the safe rule that patients who say they have pain have pain.

It is a good rule that pain, a physical sensation, always has a physical cause. If we do not know the cause, we should deplore our ignorance rather than deny the pain. The cause of pain is usually multiple; several subthreshold factors combine to give threshold stimulation. Often the cause which seems most likely is only one of the effects of an unknown common cause. In this sense every pain is psychogenic because it always has a background of dislike and is influenced by the emotional state. But we are taught that the subconscious mind tries to forget other things it does not like, and pains that we have had are so easily forgotten that we cannot even imagine them.

There is a theory that many of these pains are tension pains in two senses. Emotional tension is said to transfer itself to the muscles, which become painful through excessive contraction of fibrils. But Taverner (1954) has shown electromyographically that fibrillation is not intensified in muscles which are painful.

Visceral and Somatic Manifestations of Cerebral Disease.

Psychalgia should not be diagnosed without other evidence of neurosis, and a careful history should be taken to make sure that the pain came after the emotional disorder. Though Fletcher and Jacobs (1955) think the term psychogenic rheumatism should not be used, they state that it accurately describes 4% of their patients. I agree; but it is real and not sham pain; true somatic pain mechanisms are activated.

During hypnosis skin sensitivity can be abolished (West *et alii*, 1952). Under the hypnotic influence of tribal ceremonial the Fijians dance through fire without harm to their feet (Purves Stewart and Waterston, 1935). If a hypnotized patient is touched with a pencil and told that the skin has been burned, the spot may be painful afterwards and a blister may develop (Hadfield, 1917). Here the subconscious mind arouses real pain through organic sensory mechanisms. In true hysteria (which is self-hypnosis) the tissues can be affected in the same way.

In a patient with a gastrostomy, emotion caused swelling of the gastric mucosa, which became painful when it was lightly stroked (Wolf and Wolff, 1943). Here a combination of two subthreshold factors was necessary to generate gastric pain. With repeated emotional upsets the engorged and hyperalgesic mucosa may become habitually painful. Later the mechanism may come to depend less on emotion and more on other factors (unsuitable food, physical exhaustion). The disordered stomach may then induce tenderness of the abdominal wall, which adds to the total pain.

In producing gastro-intestinal engorgement and ulceration, emotion uses an organic pathway which is common to man and animals. Brown-Séquard (1876) cauterized a dog's frontal lobes and it developed a perforating gastric ulcer. Keller (1936) and Durante (1916) produced ulcers in rabbits and dogs by cutting the splanchnic nerves. Similar experiments have been performed on monkeys (French *et alii*, 1954) and rats (Tedeschi, 1944).

In man, Rokitansky (1841) first attributed gastric ulceration to intracranial disease. During the last few years it has been reported to follow frontal lobotomy (Arteta, 1951; Logan and Bobowiec, 1952) and intracranial lesions of many kinds (Strassman, 1927; Robinson, 1953; King and Reganis, 1953).

Neurogenic Joint Pains.

In the case reported by Wolf and Wolff (1943) the gastric pain was not directly due to emotion, but to inflammation induced by emotion acting in the same way as an organic cerebral disorder. Even then the additional factor of light stroking was necessary. Similarly, I have often seen the pain and swelling of rheumatoid polyarthritis made worse by worry; occasionally the onset of the disease has been precipitated by it.

CASE V.—A business man, aged fifty-three years, who had always been healthy, lost a large fortune in 1932. During a long railway trip alone from Melbourne to North Queensland he realized the full magnitude of the disaster, and worried as he had never worried before. On arrival he first noticed muscular stiffness; in a few days several joints were painful and swollen. He was crippled with polyarthritis until his death eighteen years later.

CASE VI.—A man, aged forty-three years, died from Huntington's chorea which ran a rapid course. Three months before his death polyarthritis first appeared. His knees, ankles, wrists and elbows were swollen and painful.

In Case V the pain could be called psychogenic. Worry acted like the organic nervous disease in Case VI to precipitate organic inflammation in many joints. Polyarthritis has been reported to complicate other central nervous diseases (Rimbaud *et alii*, 1947; Ravault *et alii*, 1949; Weil *et alii*, 1945; Hoff, 1951; Hart and Husain, 1952). The mechanism is unknown, but, like the mechanism which produces gastric inflammation, it acts through organic nervous channels.

CASE VII.—A man, aged forty-three years, referred by Dr. R. S. Hooper, noticed painful stiffness of shoulders and knees a few months after a second operation for a simple pituitary cyst. He was impotent and subject to domestic and financial worry. None of the joints were swollen and the shoulders and knees had full range. The usual fibrositic spots were tender and were infiltrated with procaine (Kelly, 1947). The pain was completely relieved for more than two months.

CASE VIII.—An unmarried woman, aged fifty-three years, was referred by Dr. J. Jens; she complained of pain and stiffness of shoulders, neck, hips and knees, of three months' duration. She had been under great strain for years looking after her paralysed mother and an office job. A schoolteacher sister is emotionally unstable and has had several breakdowns. The patient had had no relief from osteopathy, physiotherapy or a trial of "Butazolidin" (0·6 gramme daily for ten days). On examination of the patient there was no swelling of any joints, but the range of shoulders and neck was restricted. Fibrositic lesions were detected in the muscles by palpation. "Butazolidin", 0·4 gramme daily, reduced the symptoms for two weeks, then they relapsed. After a break of three weeks "Butazolidin" was prescribed again and gave almost complete relief. The dose was gradually reduced. During the next twelve months two relapses occurred, which were overcome by a three weeks' withdrawal and retrial. Finally the dose was reduced almost to nothing and so the drug was withdrawn. The cure is complete.

In Case VII there was no swelling of joints, but multiple arthralgia followed an operation on the brain. When multiple arthralgia follows worry (Case VIII) it is equally an organic disorder, produced by the same mechanism through organic channels. Both patients were relieved by specific antirheumatic treatment when other methods had failed. Wechsler (1935), who reported 16 cases of non-gastric abdominal pain due to cortical lesions (mostly frontal), wrote as follows:

> Since it has been shown that abdominal pain can and does occur on stimulation or irritation or pathologic involvement of the cortex and possibly of other regions, it is quite probable that the hysterical abdominal pain is the expression of a psychophysiogenic process and that the hysterical patient suffers neurogenic cerebral pain.

Intractable pain from damage to nervous tissues (thalamic syndrome, trigeminal neuralgia) is often intensified by emotion. A patient with a tumour of the *foramen magnum* first felt tingling in the arm during emotional strain (Symonds and Meadows, 1937). A patient with causalgia felt a throb of pain when he saw two motor-cars narrowly avert a collision (Sunderland and Kelly, 1948). The emotion intensifies the physical pain and does not generate a new kind of psychic pain. Elhardt (1945) stated that intractable pain in a war wound was increased more constantly by sorrow (92% of times) and worry (90%) than by anger (55%).

Psychoneurotics Have Normal Cutaneous Pain Thresholds.

We often read that the psychoneurotic patient's pain-perception threshold has been lowered; that he is generally hypersensitive through excessive activity of the central nervous system. When a neurotic patient suffers from pain, however, he has painful discrete lesions which resemble the lesions of fibrositis (Cases VII and VIII). In attempts to measure pain thresholds, nearly every worker on pain has evolved some sort of a dolorimeter (Goetzl *et alii*, 1943). Most of the instruments have been designed to measure cutaneous pain; Head (1894) and Gluzek (1944) used instruments to record deep pain. Libman (1934) tested his patients by digital pressure on the styloid process. Though the thumb may seem less scientific than a graded instrument, its sensitive pad is more reliable than a metal rod when muscle has to be compressed against bone, or when a spot has to be accurately localized.

Hardy *et alii* (1943) generated pain by focusing heat on the skin with a lens. The threshold, which could be raised with analgesic drugs, was the same in a nervous as in a phlegmatic patient. Their results were confirmed by Edmonds (1947), by Chapman *et alii* (1947), and by Schilling and Musser (1948). The pain-perception threshold of these patients is not the same as the reaction threshold. This is often lowered in the psychoneurotic patient, who is more likely to show that he is feeling a less intense stimulus.

Hallucination or Delusion?

We have seen that there is a mechanism by which cerebral disorders—doubtless acting with other factors—may precipitate somatic pain. There are three other possible explanations of this kind of pain:

1. It is purely central, being due to activation of the central pain mechanism.

2. It is imagined, either to escape from difficulties or for a symbolic purpose. That is, it is an hallucination.

3. A non-painful unpleasant sensation is mistakenly called pain; it is a delusion.

Central Pain.

Cerebral vascular diseases or tumours sometimes cause severe pain in the corresponding limbs (Penfield and

Gage, 1933; Walker, 1943). This is probably due in part to misinterpretation of normal sensory impulses. In health the sensory cortex is continuously receiving from the periphery a standard pattern of impulses. The cortex will not recognize pain unless it notices a change in the pattern. In disease of the thalamus the pattern is disorganized; and in some cortical diseases integration is out of tune, so that normal impulses from the periphery induce pain.

Hallucination.

Is the pain an hallucination? Hallucinations of other kinds—visual, auditory, tactile—are symptoms of profound psychosis; and our patient is not psychotic. His pain threshold is normal; and to questions he always gives the same answer—that he feels the pain. The patient may not look ill; he may speak of his pain in a detached way, which the practitioner cites as proof that it is not real. But nervousness or apprehensiveness is also held to deny the reality of the pain; the disbelieving practitioner has it both ways. Other hallucinations we can test for ourselves; if we cannot see the pink elephant, we judge that the patient who claims to see it has an hallucination. But we cannot test pain in this way; it is a symptom of disease, and we who are attempting to judge are in good health.

Delusion.

Is the pain a delusion? The patient may have hyperalgesic spots where mild pressure is felt as pain, but this is not a delusion. The thalamic syndrome may cause a fly alighting on the skin to feel like a red-hot coal. But this is true pain, because the central pain mechanism records it. Writers have suggested that the patient is mistakenly regarding as pain an unpleasant but non-painful symptom. This is a hazardous and improbable assumption. Every child at an early age is taught to distinguish between pain and other feelings of sickness. A natural question from a mother to a tiny child is, "Have you any pain?", and a natural reply of the child is, "No, but it feels nasty".

Exaggeration of Symptoms.

Malingering is very uncommon and can almost be left out of the calculations. But many patients exaggerate real symptoms, and experience is required in detecting these. The good doctor will make a mental note of it, but should never accuse the patient of exaggeration, because he may be wrong.

CASE IX.—A woman, aged forty-five years, complained of "dreadful" pains in neck and shoulders which followed an attack of acute polyarthritis. They were relieved with "Butazolidin", but relapsed and became "dreadful" again when her son went to hospital to have a "serious" operation. When I asked what the operation was she said: "Hæmorrhoids and fistula." Then in my own mind I qualified the word "dreadful". A second trial of "Butazolidin" relieved the pains again.

Treatment: "Butazolidin" and Procaine.

Treatment by giving the patient insight into his pain is seldom helpful (O'Neill, 1955; Fletcher and Jacobs, 1955; Sundt, 1955; Tegner, 1955). In many instances the pain is rheumatic; more than one-half of the patients with multiple pains can be relieved with "Butazolidin" (Kelly, 1954). A commencing dose of 0·3 gramme per day has results as good as the higher doses, and toxicity is less common (Kelly, 1955). Many patients respond at second or third trials after being apparently refractory. Relapses after early relief can be overcome by withdrawing the drug and starting again (Cases III and VIII). "Butazolidin" should not be given to patients aged over sixty-five years, or to those with gastro-intestinal or cardiovascular disorders.

One in every three patients with muscular pains is amenable to treatment by procaine infiltration of fibrositic lesions (Cases II and VII). But antirheumatic treatment is unavailing for one in every three; these patients are usually the most emotional. The wise and sympathetic physician will not discard them, but will supervise treatment with inexpensive placebos and palliatives. There is a standard joke about rheumatologists whose patients never die and never get well. But these patients need someone with the right temperament to watch over them. Clifford Allbutt once said that the job of the doctor was occasionally to cure, sometimes to alleviate, but always to comfort.

Summary.

There is no proof that idea of a pain can evoke a pain.

The belief that it can do so leads to carelessness in diagnosis and fastens stigma on the patient.

Deep somatic pain spreads widely and radiates in patterns which do not conform to the dermatomes.

In those patients with unexplained pain who are emotionally unstable, the pain nearly always precedes the mental distress. Unrelieved pain is exhausting to body and mind.

There are no hallucinations or delusions of pain except in the insane; occasionally emotion or organic cerebral disorder precipitates articular or muscular disease.

Two-thirds of the patients can be relieved by "Butazolidin" or by injections of procaine. The others should be handled with patience and sympathy.

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THE MORTALITY IN AUSTRALIA FROM SYPHILIS.

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IN this paper, the mortality in Australia from syphilis over the years 1908 to 1950 is analysed by the use of data from *Demography*, the annual bulletin of the Bureau of Census and Statistics, Canberra. In addition, the other venereal diseases are briefly mentioned as unimportant causes of mortality in Australia.

Definitions.

Syphilis has not been included among the infectious diseases in this series, largely for the sake of convenience. The "International List of Causes of Death" has assigned more of the deaths to syphilis in later revisions (the fifth and the sixth) than in earlier revisions. In all revisions there has been a rubric in the class of infectious diseases, to which deaths from congenital syphilis, acute syphilitic disease, therapeutic accidents and the like would be assigned. However, before the fifth decennial revision of the list in 1938, deaths from locomotor ataxia (*tabes dorsalis*) and general paralysis of the insane were assigned to rubrics in the class of diseases of the nervous system. Deaths from aneurysm of the aorta were assigned by the fourth revision of the list in 1929 to a rubric "aneurysm", and cannot be identified positively as syphilitic. In accordance with the fifth and sixth revisions of the list, unqualified "aneurysm" is taken to mean syphilitic aneurysm. Therefore it seems preferable for the purposes of this discussion to omit the aneurysms.

Syphilis (All Forms Excluding Aneurysm of the Aorta).

In Table I are set out the death rates from syphilis. In any period, say that from 1911 to 1920, the mortality at ages under five years is higher than in the next age group. The mortality then increases throughout life until about the age of sixty-five years, after which there is a decline. As we shall see in a later section, the mortality is at younger ages almost entirely due to congenital syphilis; in early adult life it is possibly due to acute and congenital syphilis. Finally, in adult life *tabes dorsalis* (progressive locomotor ataxia) and general paralysis of the insane are the predominant forms.

There is at every age in every period a high masculinity —that is, the male rates are higher than the corresponding female rates. In adult life, this can well be interpreted as reflecting social habits and the relative female immunity to syphilitic infections; but in childhood only the second of these can be of importance. When any age group is considered there have been definite declines in mortality at all ages. The declines at ages under five years are especially notable.

Tabes Dorsalis (Progressive Locomotor Ataxia).

In Table II are given the death rates from *tabes dorsalis*. Similar remarks apply to this tables as to Table I. There have been pronounced declines at all ages, there is a marked masculinity, and the rates reach a maximum somewhere about the age of sixty-five years in either sex.

General Paralysis of the Insane.

In Table III are given the death rates from general paralysis of the insane. Once again there is a pronounced masculinity, and considerable declines are evident in every age group.

Congenital and Other or Unspecified Forms of Syphilis.

Table IV gives the death rates from those forms of syphilis responsible for deaths other than the special nervous forms already considered, so that congenital syphilis is included here. Aneurysm of the aorta has not been included. Therapeutic accidents occurring in the

TABLE I.

The Mortality in Australia from Syphilis (Excluding Aneurysm of the Aorta).

Period.	Sex.	Deaths per Million *per Annum* at Ages (Years).									
		0 to 4.	5 to 14.	15 to 24.	25 to 34.	35 to 44.	45 to 54.	55 to 64.	65 to 74.	75 and Over.	All Ages.
1908 to 1910	M.	279	2	10	42	188	282	305	255	242	121
1911 to 1920	M.	191	4	13	59	177	298	298	257	146	117
1921 to 1930	M.	80	5	7	36	143	221	247	236	131	87
1931 to 1940	M.	40	2	5	18	92	178	246	238	156	74
1941 to 1945	M.	19	2	3	8	34	104	154	152	102	41
1946 to 1950	M.	9	0	6	6	18	53	99	128	72	29
1908 to 1910	F.	196	4	7	15	42	63	65	78	127	46
1911 to 1920	F.	155	3	8	13	40	63	64	29	43	38
1921 to 1930	F.	70	2	5	12	29	52	47	51	39	26
1931 to 1940	F.	30	2	4	9	21	37	46	46	28	19
1941 to 1945	F.	12	1	2	3	9	28	35	32	10	11
1946 to 1950	F.	6	1	0	3	6	17	23	18	12	6

TABLE II.

The Mortality in Australia from Progressive Locomotor Ataxia.

Period.	Sex.	Deaths per Million *per Annum* at Ages (Years).						
		25 to 34.	35 to 44.	45 to 54.	55 to 64.	65 to 74.	75 and Over.	All Ages.
1908 to 1910	M.	3	18	67	93	112	88	19
1911 to 1920	M.	5	22	77	133	131	81	25
1921 to 1930	M.	1	12	48	100	110	62	19
1931 to 1940	M.	0	5	25	53	89	58	13
1941 to 1945	M.	1	4	13	33	35	33	7
1946 to 1950	M.	0	0	7	24	40	16	6
1908 to 1910	F.	1	7	9	18	22	13	3
1911 to 1920	F.	0	6	13	29	15	12	4
1921 to 1930	F.	0	3	14	13	21	7	4
1931 to 1940	F.	0	1	4	8	9	6	2
1941 to 1945	F.	0	0	1	2	3	2	1
1946 to 1950	F.	0	1	1	5	4	5	1

TABLE III.

The Mortality in Australia from General Paralysis of the Insane.

Period.	Sex.	Deaths per Million *per Annum* at Ages (Years).						
		25 to 34.	35 to 44.	45 to 54.	55 to 64.	65 to 74.	75 and Over.	All Ages.
1908 to 1910	M.	32	144	177	170	112	121	56
1911 to 1920	M.	37	128	174	111	52	28	51
1921 to 1930	M.	24	98	117	75	49	32	38
1931 to 1940	M.	10	54	70	66	33	6	24
1941 to 1945	M.	3	22	57	53	32	8	17
1946 to 1950	M.	2	10	25	39	33	7	11
1908 to 1910	F.	9	21	31	33	45	101	12
1911 to 1920	F.	6	22	30	18	10	25	9
1921 to 1930	F.	5	12	18	14	9	18	6
1931 to 1940	F.	3	9	13	11	11	12	5
1941 to 1945	F.	1	6	11	14	7	2	4
1946 to 1950	F.	2	2	7	7	5	2	2

TABLE IV.

The Mortality in Australia from Congenital and Unspecified Forms of Syphilis.

Period.	Sex.	Deaths per Million *per Annum* at Ages (Years).									
		0 to 4.	5 to 14.	15 to 24.	25 to 34.	35 to 44.	45 to 54.	55 to 64.	65 to 74.	75 and Over.	All Ages.
1908 to 1910	M.	279	2	6	7	26	38	42	31	33	46
1911 to 1920	M.	191	3	5	17	27	47	54	74	37	41
1921 to 1930	M.	80	4	4	11	33	56	72	77	37	30
1931 to 1940	M.	40	2	3	8	33	83	128	117	91	37
1941 to 1945	M.	19	2	2	2	8	34	68	85	61	17
1946 to 1950	M.	9	0	4	4	7	21	36	55	49	12
1908 to 1910	F.	196	2	5	5	14	23	14	11	13	31
1911 to 1920	F.	155	3	5	7	12	20	17	4	6	25
1921 to 1930	F.	70	2	3	7	14	20	20	21	14	16
1931 to 1940	F.	30	2	3	6	10	20	27	26	10	12
1941 to 1945	F.	11	1	2	2	3	16	19	22	6	6
1946 to 1950	F.	6	1	0	1	3	9	11	9	5	5

treatment of syphilis would be referred to this rubric, as also would any deaths, certified as being due to gumma, luetic disease, tertiary syphilis and the like.

It is evident from Table IV that there has been a great decline in congenital syphilis. Declines have occurred in the rates at all other ages, but are not so large. In fact, the declines are temporarily obscured in the age groups over forty-five years by some change in assignment of deaths to this rubric about 1927. Thus the male deaths from general paralysis of the insane were in 1926 and the following years 124, 136, 102, 92, 58 and 93, and from syphilis in the same years 90, 92, 122, 192, 111 and 110. Thus in 1928 there seems to have been a tendency to transfer deaths formerly assigned to general paralysis of the insane to this rubric, "syphilis".

Gonorrhœa and Other Venereal Diseases.

Gonorrhœa.

As might have been expected, deaths assigned to gonorrhœa as a cause have been few. In the six periods of Table I, the deaths of males from gonorrhœa in Australia have been four, 30, 29, 26, five and four, and the corresponding female rates 0, 19, eight, eight, eight and 0.

Lymphogranuloma Venereum.

Lymphogranuloma venereum has occasionally been noted in Australia, but has not been recorded as a cause of death.

Granuloma Inguinale.

Granuloma inguinale does not occur in the European population, although it is common in New Guinea natives and in parts of northern Australia.

Discussion.

Some clinical features of syphilis in Australia have been reviewed by Engel (1954), who gives notification rates and crude death rates by year for Australia from 1935 to 1951. He believed that "syphilis has never been a widespread or sinister disease in Australia".

The declines in the death rates from syphilis can safely be attributed to the effects of the introduction of the organic arsenicals after 1911. There do not appear to have been sufficient changes in social behaviour to suggest that we should attribute the declines to them.

Summary.

There has been a notable decline in the mortality from syphilis in Australia.

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DISSEMINATED LUPUS ERYTHEMATOSUS.

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DISSEMINATED *lupus erythematosus* is a disease with widespread systemic manifestations involving especially the serous membranes and the skin and characterized by patchy fibrinoid changes in the connective tissue.

The purpose of this paper is to record some experiences with this disease at the Johns Hopkins Hospital and to cite some of the recent publications on the subject. The hospital records of 17 recent proven cases were inspected. Information was also gathered on the teaching rounds of the Osler Clinic during the years 1951 to 1953.

Nomenclature.

The prefix "disseminated" is used to denote systemic involvement recognized clinically rather than pathologically. In the past a clear distinction has always been made between chronic discoid *lupus erythematosus* and disseminated *lupus erythematosus*. With greater experience and newer methods of diagnosis this distinction is now less clearly drawn. In some cases at least chronic discoid *lupus erythematosus* has proceeded to disseminated *lupus erythematosus* while under observation.

Historical Review.

In 1895 Osler described the clinical course of disseminated *lupus erythematosus*. Libman and Sacks in 1924 recognized an associated endocarditis. Klemperer and Baehr (1942) have contributed to the pathology of the disease in recent years. In 1944 and subsequently Rich (1946-1947) made important observations on the role of hypersensitivity in the collagen vascular diseases, among which disseminated *lupus erythematosus* is included. In 1948 Hargraves described the "L.E." cell, which has greatly facilitated the exact clinical diagnosis of the disease.

Incidence.

About 15 to 20 cases are diagnosed each year in the Johns Hopkins Hospital. Some of these patients are referred for diagnosis when the disease has been already suspected, and hence no true figures for the incidence are available. There is a high index of suspicion for the disease at all levels of the medical staff, and probably few cases escape diagnosis.

Ætiology.

The cause of the disease is unknown. The following facts have been observed.

1. It occurs predominantly in females in the ratio of four to one for males. The great majority of cases occur between the ages of ten and forty years.

2. There is a relationship between the disseminated and the discoid forms. The discoid lesion occurs in up to one-third of cases either before or during the course of the disseminated disease.

3. Certain physical and chemical agents appear to precipitate the onset of symptoms—for example, exposure to sunlight, treatment with gold or bismuth, sensitivity reactions to sulphonamides.

4. A significant tuberculous infection, usually active focal lymphadenitis, is found at biopsy or post-mortem examination in about 20% of cases.

5. A positive or equivocal serological finding for syphilis is found in 20% of cases. There is no history of syphilis and the treponema-immobilization test gives negative results in the majority of cases.

Pathological and Pathogenic Relationship to the Diffuse Collagen Diseases.

The term "diffuse collagen disease" is used to denote a group of diseases, usually with distinct clinical patterns, which share certain histological changes in connective tissue. For the present purpose, the term will include disseminated *lupus erythematosus*, *periarteritis nodosa*, rheumatic fever, rheumatoid arthritis and serum sickness. Many authorities include dermatomyositis and scleroderma under this heading. The following comments refer particularly to the first of these two groups of diseases.

Clinically, these diseases often have some manifestations in common—for example, fever, arthralgia, arthritis, erythema and, less often, purpura, Raynaud's phenomena, myocarditis, polyserositis and pulmonary and renal lesions. When the patient is first examined a definitive diagnosis is sometimes difficult other than "diffuse collagen disease"; but under further interrogation and observation a distinctive clinical syndrome emerges.

The characteristic pathological changes in the collagen diseases involve the connective tissue. In disseminated

lupus erythematosus the gross changes are usually meagre. Effusion or adhesions may be present in the serous cavities and there may be evidence of lymphoid hyperplasia and splenomegaly. On microscopic examination of sections of viscera, muscles or glands, focal areas of œdema and of degenerative or proliferative changes in the cellular elements of connective tissue are noted, especially around small arteries. The ground substance is abnormally prominent, taking on an intense eosinophilic colour with the routine hematoxylin-eosin stain. It undergoes an amorphous change, fusing with some of the degenerated cellular elements (fibrinoid degeneration). Leucocytic infiltration occurs in and around these foci.

These lesions may be compared with some of the characteristic lesions of the other collagen diseases. In *periarteritis nodosa* the connective tissue in and around the walls of medium-sized and small arteries is primarily affected. Necrosis, proliferation and fibrinoid degeneration are seen with obliteration of the lumen, in some cases, due either to thrombosis or to proliferative change in the vessel wall. In rheumatic fever multiple lesions are found in all layers of the heart. In focal areas the connective tissue fibres swell, degenerate and become fused with the amorphous ground substance. Surrounded by mononuclear and large, irregular, multinuclear cells, this is called the Aschoff nodule. The subcutaneous nodule of rheumatic fever consists of a central focus of fibrinoid degeneration surrounded by palisades of proliferating fibroblasts. In rheumatoid arthritis, œdema, generalized proliferation and focal degeneration occur in the synovium and subsynovial connective tissue. Cardiac lesions resembling those of rheumatic fever have been described. Some authorities believe that the variations from one disease to the other in the collagen group are of distribution and degree.

In his Harvey Lecture of November 21, 1946, Rich discussed the pathogenetic relationships between these diseases. He demonstrated the widespread vascular lesions of *periarteritis nodosa* in patients who died after systemic hypersensitivity reactions to foreign serum and sulphonamides. He reproduced the lesions in rabbits rendered hypersensitive by intravenous injections of foreign protein. He was surprised to find, in addition, lesions in the hearts of these rabbits resembling the Aschoff nodule of rheumatic fever. Hawn and Janeway (1947) have confirmed Rich's work. They sensitized their rabbits with albumin and globulin fractions of bovine plasma. The albumin fraction produced lesions of *periarteritis nodosa*, the globulin fraction lesions resembling those of acute glomerulonephritis. Others have observed vascular changes resembling *periarteritis nodosa* in the rabbit and rat when hypertension has been induced by the Goldblatt method of reducing renal blood flow.

This work sugests a pathogenesis for some of the collagen diseases. The ætiological agent remains unknown. Physical and chemical agents, bacterial antigens and foreign sera may play a part. The location of the lesions—that is, the site of tissue antibodies—may be determined by hereditary factors. Nothing is known of the factors governing the extent of tissue reaction to the ætiological agent in the individual case.

Clinical Features.

The earliest symptoms of disseminated *lupus erythematosus* are usually non-specific, and often not serious enough, in the mind of the patient, to require an immediate visit to the physician.

In more than 50% of the cases the first symptom the patient associates with the onset of his disease has been arthralgia. This may range from vague and persistent aches and pains to short-lived and disabling attacks of joint pain in the limbs. In most cases the objective signs of arthritis are absent or minimal and transient. "Virus pneumonia", pleurisy, obscure fever and weight loss may be other early manifestations. In others, transient erythemata sometimes associated with hypersensitivity reactions or exposure to sunlight are the earliest symptoms. Some patients trace the onset of their illness to recurrent attacks of parotid swelling or to thrombophlebitis or the appearance of Raynaud's phenomena. The interval between these early symptoms and the diagnosis of disseminated *lupus erythematosus* is usually about two years.

The majority of cases emerge, sooner or later, with a pattern of symptoms and signs which is characteristic (Tumulty and Harvey, 1949). Arthralgia and arthritis occur in nearly every case. An erythema—which may be fleeting—appears at some stage of the disease. The rash has the characteristic "butterfly" distribution in about one-third of the cases. Fever, anorexia, malaise and weight loss appear as the disease progresses. The weight loss may be obscured by nephritic œdema. Cough, sputum, chest pain and fever may indicate pneumonitis or a pleural or pericardial effusion. It is remarkable how these last manifestations occur or persist in some cases without localizing symptoms. Hæmorrhagic phenomena may appear—for example, epistaxis, bleeding gums, menorrhagia, ecchymoses or purpura.

A complete physical examination is indicated whenever the diagnosis of disseminated *lupus erythematosus* is considered. The body temperature is often elevated on serial readings, especially during an acute exacerbation of the disease. The blood pressure is usually normal. The skin, conjunctiva or mucous membranes may exhibit erythematous, inflammatory or vesicular lesions. In about one-half of the cases, examination of the retina reveals significant vascular changes, exudates or hæmorrhages. Lymphadenopathy and splenomegaly may be found. The liver is often palpable. Findings compatible with pleural effusion or pneumonitis are found at some stage of the disease in most cases. Examination of the precordium usually reveals little apart from an apical systolic murmur. Transient friction may be heard, or the precordial dulness may be increased owing to pericardial effusion. The joints of the limbs show, in most cases, little objective evidence of arthritic change. However, in some patients, there are pronounced periarticular fibrosis, limitation of movement and muscular atrophy.

Laboratory Observations.

In disseminated *lupus erythematosus* there is usually a moderately severe normocytic hypochromic anæmia (that is, a hæmoglobin value less than 10 grammes per 100 millilitres). In about half the cases leucopenia is present (less than 5000 leucocytes per cubic millimetre) and, more rarely, thrombocytopenia. The differential leucocyte count is within normal range in most cases. No signficant eosinophilia is observed. The erythrocyte sedimentation rate is elevated above 20 millimetres in one hour (Wintrobe's method) in nearly all cases. Albuminuria is found in about half the cases, usually accompanied by microscopically evident hæmaturia. Both these findings may be transient.

The serological tests for syphilis give positive or equivocal results in about 20% of patients. This finding may also be reversible without anti-luetic therapy. The treponema-immobilization test gives a negative result. The total serum protein content may be normal, but the albumin-globulin ratio is altered in nearly all cases, actual inversion occurring in about two out of three.

Renal and liver function tests may reveal mild or moderate impairment, compatible with the findings enumerated above.

Radiological and fluoroscopic examination of the chest may reveal pleural and pericardial effusions or diffuse pulmonary infiltrations. These changes are present in at least two-thirds of the patients on serial examinations.

Diagnosis.

A clinical diagnosis of disseminated *lupus erythematosus* may be made with some confidence in the presence of the characteristic facial skin rash and several of the other manifestations of the disease. The diagnosis may be sensibly considered in relation to a persistent or remittent systemic disease with fever and in addition arthralgia,

polyserositis, non-bacterial endocarditis or obscure blood dyscrasia when a thorough investigation has failed to provide any other ætiological explanation.

In 1948 Hargraves described the L.E. cell in special preparations of bone marrow of patients with disseminated *lupus erythematosus*. In 1949 and subsequently (Haserick, 1951; Anonymous, 1953) other methods have been described for the demonstration of the L.E. cell in the buffy coat of centrifuged peripheral blood of patients with the disease, and also in the cellular residue of clotted peripheral blood from which the serum has been discarded. It has also been demonstrated in the sediment of mixtures of patients' serum and the buffy coat of normal donors' blood.

The L.E. cell is a leucocyte, probably an adult neutrophile cell, which has within it an engulfed mass of homogeneous basophilic material, the nucleus being displaced into an eccentric position. In addition, the L.E. rosette is described, which is a clump of polymorphonuclear cells surrounding a free mass of this same homogeneous material. The L.E. cell is considered diagnostic, and the L.E. rosette strongly suggestive, of disseminated *lupus erythematosus*. Absence of L.E. cells or rosettes from a single preparation is of little significance; on occasion the characteristic cell is demonstrated only after several attempts. The L.E. cell may be found early or late in the disease, and appears to bear little relationship to a clinical evaluation of the stage of the disease.

At medical staff rounds in February, 1953, at the Johns Hopkins Hospital, C. L. Conley reported that his laboratory had examined approximately 1760 L.E. cell preparations from 1000 patients, 65 of whom had clinically evident disseminated *lupus erythematosus*. In 58 of the latter the L.E. cell was found. In his experience the L.E. cell was specific for disseminated *lupus erythematosus*.

When the disease is suspected the following helpful investigations are usually carried out: (i) a complete blood count and estimation of the erythrocyte sedimentation rate; (ii) examination of the urine by the usual methods; (iii) estimation of the serum non-protein nitrogen content, the serum protein content and the albumin-globulin ratio; (iv) a serological test for syphilis; (v) an L.E. cell preparation.

Further blood chemical determinations are usually carried out to evaluate renal and liver function as a baseline before therapy is instituted. In order to exclude complicating bacterial infections, blood cultures are attempted, and, if indicated, cultures are attempted from throat swabbings, sputum or gastric contents. An X-ray examination of the chest is always made.

Course and Prognosis.

In general, the course of the disease is progressive. If it persists as an acute disease, deterioration is rapid, with fever, weight loss and azotæmia. Remissions of the acute symptoms may occur, though further relapses are the rule. In the less acute cases the condition may go into remission of unpredictable length and may then relapse into the same stage as before. Again, progressive renal impairment may occur with each relapse. Congestive cardiac failure is rare. Severe anæmia, responding only to repeated blood transfusions, may occur. Thrombocytopenia with purpura may require splenectomy. Commonly, complicating infections (for example, tuberculosis, pneumonia, septicæmia) compromise the patient's chance of remission.

The L.E. preparation has provided a more sensitive method of diagnosis and has uncovered some cases early in the course of the disease (for example, during the investigation of a positive serological finding for syphilis in an otherwise apparently healthy person). As these cases are observed, the present-day concept of the almost inevitable progression of the disease may be altered.

Treatment.

It appears clear that if high enough doses of either of the hormones ACTH or cortisone are used the disease process may be suppressed, temporarily at least, in most cases (Soffer and Bader, 1952; Shulman, 1954). It has not yet been ascertained whether the ultimate prognosis can be altered.

According to Shulman (1954), a patient with symptoms is admitted to hospital and studied with particular reference to renal function. Cortisone or ACTH therapy is started in doses sufficient to suppress most of the symptoms; it is then gradually withdrawn over a two-week period. Over two-thirds of the patients experience a relapse of symptoms within a month of withdrawal of the hormone, but most of these lose their symptoms without further steroid hormone treatment at that stage. If the return of the symptoms persists for over a month, the patient is usually given another course of steroid hormone till the symptoms are largely suppressed; the dosage is then reduced to a maintenance level over a two-week period. The usual precautions are taken to avoid the undesirable side-effects of therapy with these hormones.

Summary.

Disseminated *lupus erythematosus*, described by Osler in 1895, remained a medical curiosity until the work of Klemperer revived the interest of the clinicians. This interest has encompassed all the diseases of the "diffuse collagen group", though the recent diagnostic L.E. cell phenomenon of Hargraves has focused attention on disseminated *lupus erythematosus*. Hence the disease is being more often diagnosed, and Harvey *et alii* (1954), of the Johns Hopkins Hospital, have recently described 138 cases, the last 90 of these seen in the period from 1949 to 1954.

The disease usually occurs in young women, and is characterized by arthralgia, fever, erythematous eruptions, malaise and weight loss. However, in the early stages, the systemic nature of the disease may not be apparent, and this may lead to a delay in diagnosis. Anæmia, elevated sedimentation rate, plasma protein abnormalities and albuminuria are often found. If an awareness of the disease exists, the diagnosis may be suspected clinically and proven by the demonstration of the L.E. cell.

The course of the disease is characterized by remissions even without treatment by ACTH or cortisone. When viewed in retrospect to the probable date of onset, the disease has a long course of five or ten or more years, and death is often due to renal failure or complicating bacterial infections. ACTH and cortisone may hasten a remission of symptoms, but their effect on the over-all course of the disease has not yet been determined.

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Reports of Cases.

OCULAR LESIONS ASSOCIATED WITH BRUCELLOSIS: REPORTS OF TWO CASES.[1]

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THE association of ocular lesions with brucellosis receives small reference in standard text-books, with the exception of Walsh (1947). Although the first human case—one of bilateral optic neuritis and oculorotary paralysis—appears to have been reported by Lemaire in 1924 (Green, 1939), it is mainly in the last ten years or so that ophthalmic literature includes much study of the relationship. Most of the references are in American literature, with some from Europe; but Foggitt (1954) reported a case in England of brucellosis associated with anterior uveitis in one eye, later followed by *periphlebitis retinæ* in the other. In an excellent survey of 413 cases of undoubted Brucella infection in Mexico City (where *Brucella melitensis* is the common species) Solanes, Heatley, Arenas and Ibarra (1953) found 12 pure ocular lesions (eight of them uveitis) and 48 neuro-ophthalmic disorders (mainly optic nerve lesions)—that is, an incidence of 14·5%—while Woods (1951) records ". . . the almost conclusive evidence of brucellosis as a cause of endogenous ocular disease, keratitis and uveitis . . .".

As the list of lesions for which brucellosis may be a possible cause includes keratitis, iridocyclitis, uveitis, retinopathies, papillitis, optic neuritis and ocular palsies, it is thought advisable that brucellosis be at least considered when the necessary investigations of such cases are being conducted. Brucellosis (undulant fever) is a not infrequent disease in this country, especially in dairying areas. It therefore seems reasonable to draw attention to its association with ocular lesions by recording the following cases.

Case I.

A male dairy farmer, aged twenty-four years, was referred to one of us (K.L.) by Dr. P. M. Dow, of Warragul, Victoria, on December 8, 1954. The patient complained that a "green film" had appeared over the vision of his right eye the previous week. The past history was without significance except for scarlatina at the age of ten years. General systemic examination did not now reveal any abnormality.

Examination of the right eye, which had visual acuity of 6/12, revealed a semi-opaque cornea. Slit-lamp examination showed this to be due to large lardaceous keratic precipitates which almost completely covered its posterior surface. A "flare" and floating cells were present in the anterior chamber. The pupil dilated regularly. Fundus examination revealed two patches of choroiditis in the mid-peripheral region inferiorly; one appeared to be healed, while the other, which was adjacent, was acute and active. The area of each was about that of the optic disk. The left eye appeared normal. The diagnosis was choroiditis and iridocyclitis. The local use of atropine sulphate (1%) twice a day and cortisone (0·5%) every two hours was advised.

The results of the Wassermann and Kahn tests were negative, but the *Br. abortus* agglutination test produced a positive result (1 in 160, conventional test; 1 in 320, antiglobulin test).

Further treatment was begun on December 20 with a ten-day course of tetracycline hydrochloride, 500 milligrammes given by mouth four times a day, and streptomycin, one gramme given by intramuscular injection once a day.

Improvement was rapid. The keratic precipitates lessened before the systemic treatment was begun, and by January 18, 1955, none could be detected, and the aqueous was free from "flare" and floating cells. Fundus examination now revealed two inactive choroidal lesions inferiorly. The visual acuity was almost full 6/6. The local use of atropine and cortisone was continued twice a day. The patient remained well until the middle of February, 1955, when his right eye "was not so good" (very indefinite history) and he experienced general malaise for about one week. When his eye was examined on March 1 a faint aqueous "flare" was present, and local treatment was continued. At the time of his last visit on May 17 there was no sign of active inflammation, the visual acuity was normal, and the agglutination titre had fallen to 1/40 (antiglobulin test).

Case II.

A male poultry farmer, aged twenty-seven years, who frequently handled animal offal, consulted one of us (K.L.) on March 17, 1955, complaining that for the previous three weeks his right eye had been painful, red and lachrymating. Three weeks prior to the onset of the eye symptoms he had suffered from a seven-day febrile illness with a swinging temperature of 104° F.

Examination of the right eye revealed extensive diskiform keratitis with epithelial œdema and considerable interstitial infiltration. Numerous keratic precipitates were present, as well as an aqueous "flare". The pupil was dilated regularly (atropine drops had been used for the previous ten days). The visual acuity was 6/36. The left eye was normal and had normal visual acuity.

The diagnosis was diskiform keratitis. Initial treatment with atropine drops (1%) twice a day and cortisone drops (0·5%) instilled every two hours in the affected eye was advised.

The results of the Wassermann and Kahn tests were negative, but the direct *Br. abortus* agglutination test produced a positive result to 1/2560, which is regarded as certain evidence of Brucella infection, though admittedly this may have been merely coincidental.

Further treatment, consisting of a ten-day course of tetracycline hydrochloride, 500 milligrammes four times a day given by mouth, and streptomycin, 0·5 gramme twice a day given by intramuscular injection, was commenced on March 28. His condition rapidly improved, and by April 18 the keratic precipitates and aqueous "flare" had disappeared. The deeper corneal infiltration had been absorbed, but the superficial corneal stroma was still involved. When the patient was last examined on May 17, the eye appeared normal except for a faint superficial corneal haze.

Discussion.

The unequivocal diagnosis of Brucella infection can be established only by culture of the organism, and since in practice this is beset with technical difficulties, the conclusion that a patient is suffering from brucellosis usually depends on serological evidence in support of clinical findings. If the patient presents early enough, it may be possible to demonstrate a significant rise in the titre of circulating antibody; but because of the insidious nature of the onset and the vagueness and multiplicity of the symptoms, it frequently happens that the basic level of antibody is not evaluated; hence the diagnosis rests simply, if somewhat insecurely, on a raised antibody level.

The adoption of the antiglobulin modification of the direct Brucella agglutination test (Wilson and Merrifield, 1950) has increased the sensitivity of this test and has almost certainly improved it as a means of establishing a positive diagnosis, for cases of undoubted brucellosis have been encountered in which there was a negative response to the conventional test and a positive response to the antiglobulin test. In their published series of 30 cases in which the antiglobulin test was of value, the above-

[1] Received for publication on June 2, 1955.

mentioned writers cite two patients who presented with iritis. Since then seven further cases (including the two herein recorded) have come to light in the Public Health Laboratory of the University of Melbourne; in each one there was an "antiglobulin" titre of 1 in 80 or greater. The serum from each of these patients, except that from one of the two whose cases are now reported, was submitted to the laboratory not for titration of brucella antibody, but for exclusion of lues by the Wassermann and Kahn tests, and it was only because serum from such cases is now as a routine examined for Brucella agglutinins that the probable nature of the infection was revealed.

In the light of this experience we submit that brucellosis should always be considered in cases of intraocular inflammation of obscure ætiology, emphasizing that as a masquerader *Treponema pallidum* has a very accomplished rival in each member of the genus Brucella.

Summary.

1. The association of Brucella infection with inflammatory conditions within the orbit is briefly reviewed.

2. Two cases of ocular disease probably due to Brucella infection are reported.

3. It is concluded that serum from all cases of obscure inflammatory disease within the orbit should be titrated by the direct agglutination test and its antiglobulin modification for Brucella antibody.

Acknowledgements.

Our thanks are due to Dr. P. M. Dow (Warragul) and Dr. M. Starr (Werribee) for details concerning and assistance with the treatment of the patients in Case I and Case II respectively.

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RUPTURE OF SMALL BOWEL IN ASSOCIATION WITH PROCIDENTIA.

By RICHARD NEWING, M.D. (Melbourne), B.S., F.R.C.S. (England),
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THE fragility of the small bowel and its ability to rupture without injury to the skin have been recognized since the time of Aristotle. It was a common cause of death in the Middle Ages—often from kicks of horses or blows.

The first successful recorded operations were performed by Sacherus in 1720, who repaired a subparietal rupture of the small bowel, and by Ramdohr in 1730, who successfully sutured a completely divided small bowel.

In the nineteenth century experimental procedures in dogs clarified the mode of production of these injuries, and later many outstanding surgeons pleaded for early intervention in abdominal trauma. In those times the overall mortality rate was 70%, and even now a recent figure is 50·4%.

Many cases have been reported of traumatic rupture in association with inguinal hernia, often due to direct injury to or pressure on the unprotected bowel, but sometimes occurring with injury or sudden strain remote from the hernia. It is likely that the significance of the associated hernia has been often overlooked in the literature, especially as the hernia has not, in many instances, been "down" at the time of injury. Bunge, however, has postulated a very neat explanation which can probably be applied to such cases. A sudden rise in intraabdominal pressure is invariably reflected by a rise in intraintestinal pressure. The fragile intestine is protected, fortunately, by the uniform pressure of the abdominal walls. However, if there is an unsupported peritoneal cul-de-sac, particularly if this is empty—the loop of bowel lying against this orifice will balloon into it and may rupture. The mechanism has been compared with a football inner bladder, which, on being suddenly pumped up, will "blow out" through a defect in its leather covering and may rupture.

The following case is of interest because the rupture occurred in association with another peritoneal cul-de-sac, but its mechanism is probably similar to that described. One would expect it to occur quite frequently, but few if any cases have been reported.

Clinical Record.

Mrs. A., an obese woman, aged seventy-three years, was admitted to the City General Hospital, Sheffield, on November 8, 1953, with the story that five hours previously she had slipped and fallen, and her womb had prolapsed. She was emphatic that she did not sit on the prolapsed womb. Simultaneously with the fall severe generalized abdominal pain developed and she was unable to rise. She had not vomited. Her doctor had given her morphine and tried to reduce the prolapse without avail, only causing more severe pain. However, it was subsequently reduced in hospital without much difficulty. She had suffered from a complete procidentia for many years, but it had always been replaceable and she had desired no treatment. When the patient was examined her condition was poor and she showed signs of peripheral circulatory failure. Generalized abdominal rigidity and tenderness were present, and bowel sounds were absent. She had a complete procidentia, with a large œdematous enterocele, which on being carefully replaced was very tender and caused her to feel nauseated. She had no herniæ and there were no other relevant findings. She was thought to have sustained a ruptured viscus, and resuscitative measures were commenced before operation.

At operation under general anæsthesia the abdomen was opened by a right paramedian incision. There was a large amount of non-odorous purulent free fluid with much fibrin. There was a perforation of the ileum four feet from the ileo-caecal valve, on the antemesenteric border, and measuring half an inch in diameter, with everted pouting edges. The bowel itself seemed healthy. The affected ileum was lying in the pelvis, adherent to the orifice of the enterocele, where was the obvious origin of the peritonitis. This cavity would contain the tips of three fingers, although its orifice was rather smaller. Other operative findings were cholelithiasis and diverticulosis. The perforation was closed in two layers, the peritoneal cavity sucked out and the abdomen closed without drainage.

After the operation her condition deteriorated despite treatment and she died at 9.35 p.m. on the same day.

At the post-mortem examination the operative findings were confirmed and the ileum at the site of perforation was macroscopically and microscopically healthy. There was complete prolapse of a large congested uterus, the ovaries and the Fallopian tubes. No other hernia was demonstrated.

Death was due to general peritonitis.

Comment.

It is reasonable to suppose that the mechanism of rupture postulated by Bunge probably occurred in this case—the intraabdominal pressure was suddenly raised as the patient fell, presumably with tensed abdominal musculature. The immediate onset of pain and peritonitis also suggests a "blow-out" of the intestine into the enterocele.

There was none of the temporary sealing of the rupture by the pouting mucosa, and later leak, as occurs with a more direct intestinal injury. It is possible that in similar circumstances the intestinal wall would not rupture primarily, but, as Bunge suggested, only after ten to fourteen days, as happens so disastrously in underwater blast injuries.

This case illustrates the urgency of laparotomy in any case of suspected intestinal rupture, and shows that only the simplest surgical closure and peritoneal toilet should be performed. It also illustrates how gloomy is the prognosis, even under the best circumstances, for old people overtaken by this misfortune.

Summary.

A case is reported illustrating rupture of the ileum in association with an enterocele.

Acknowledgements.

My grateful thanks are due to Mr. J. T. Chesterman and Mr. F. J. P. O'Gorman, of Sheffield, Yorkshire, for permission and encouragement in publishing this report.

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Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Transplantation of Tissues, Cartilage, Bone, Fascia, Tendon, and Muscle", by Lyndon A. Peer, M.D.; Volume I; 1955. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 10" x 6½", pp. 438, with 163 illustrations. Price: £7 8s. 6d.

Intended for the physician, surgeon and medical student.

"Hypnosis in Asthma", by A. Philip Magonet, B.Sc., M.D., C.M., with a foreword by Roger Francis Tredgold, M.A., M.D., D.P.M.; 1955. London: William Heinemann (Medical Books), Limited. 7½" x 5", pp. 96. Price: 7s. 6d.

Tredgold in the foreword states that the author has made it clear that hypnosis can be used in certain cases of asthma which have failed to respond to other methods.

"Forensic Medicine: A Textbook for Students and Practitioners", by Sir Sydney Smith, C.B.E., LL.D., M.D. (Edin.), F.R.C.P. (Edin.), D.P.H., F.R.S.E., Hon. M.D. Louvain, and Frederick Smith Fiddes, O.B.E., M.D.; Tenth Edition; 1955. London: J. and A. Churchill, Limited. 9½" x 6", pp. 656, with 173 illustrations. Price: 40s.

The first edition of this book was published in 1925.

"A New Classification of Tuberculosis with New Diagnostic Standards", by Milosh Sekulich, M.D., edited by H. Stanley Banks, M.D., F.R.C.P.; 1955. London: William Heinemann (Medical Books), Limited. 8½" x 5½", pp. 64, with many illustrations. Price: 3s. 6d.

The author has written other books on the subject.

"Whys and Wherefores in Tuberculosis", by George Day; 1955. London: The National Association for the Prevention of Tuberculosis. 8" x 5½", pp. 44. Price: 3s. 6d.

One of a series of new publications by NAPT.

"The House Physician's Handbook", by C. Allan Birch, M.D., F.R.C.P.; 1955. Edinburgh and London: E. and S. Livingstone, Limited. 7½" x 5", pp. 168. Price: 10s. 6d.

Intended for doctors in Great Britain working in regional hospitals.

"Erythromycin", by Wallace E. Herrell, M.D., M.S., F.A.C.P., with a foreword by Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D.; "Antibiotics Monographs No. 1"; 1955. New York: Medical Encyclopedia, Incorporated. New York and London: Interscience Publishers, Incorporated. 9" x 6", pp. 64. Price: $3.00.

The first of a series of monographs intended for the general practitioner.

"Industry and Tropical Health II. Proceedings of the Second Conference Industrial Council for Tropical Health, Sponsored by the Harvard School of Public Health, April 20-22, 1954, in New York and Boston"; 1955. Boston: Published by The Harvard School of Public Health for The Industrial Council for Tropical Health. 10½" x 8", pp. 266, with many illustrations. Price: $10.00 (professional rate $5.00).

The details of the conference cover 212 pages; the remainder is given over to photographs of the participants with an account of who they are, and an index.

"Clinical Interpreter: For Use with New Australian Patients", by David Pitt and John Kiernan; 1955. Ripponlea: Published by M. J. Hardy. 8" x 5", pp. 38. Price: 7s. 6d.

Words and questions in English, French, German and Italian set out in parallel columns.

"Atlas of Outline Drawings for Vertebrate Anatomy", by Samuel Eddy, Clarence P. Oliver and John P. Turner; Second Edition; 1955. New York: John Wiley and Sons, Incorporated. London: Chapman and Hall, Limited. 11" x 8½", pp. 106. Price: $3.25.

Consists of unlabelled outline drawings to aid the student studying the anatomy of the type of animals commonly dissected in vertebrate anatomy.

"Textbook of Occupational Therapy: With Chief Reference to Psychological Medicine", by Eamon N. M. O'Sullivan, B.A., M.B., D.P.M.; 1955. London: H. K. Lewis and Company, Limited. 8½" x 5½", pp. 330. Price: 21s.

The author has written primarily, though not solely, for those connected with mental hospitals.

"Clinical Biochemistry", by Abraham Cantarow, M.D., and Max Trumper, Ph.D.; Fifth Edition; 1955. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 9½" x 6", pp. 772, with many illustrations. Price: £4 10s.

The purpose of the book is to bridge the gap between the literature of "so-called 'fundamental' biochemistry and physiology and that of clinical medicine".

"Collected Papers on Aviation Medicine", presented at Aeromedical Panel Meetings of the Advisory Group for Aeronautical Research and Development, Palais de Chaillot, Paris; 1955. London: Butterworth's Scientific Publications. 10" x 6", pp. 218. Price: 37s. 6d.

The papers are eighteen in number. The book is described as "Agardograph Number 6".

"Handbook of Pediatrics", by Henry K. Silver, M.D., C. Henry Kempe, M.D., and Henry B. Bruyn, M.D.; 1955. California: Lange Medical Publications. 7" x 4", pp. 556. Price: $3.00.

Intended to be of use in the diagnosis and management of pædiatric disorders and to supplement rather than replace text-books.

"The Medical Annual: A Year Book of Treatment and Practitioners' Index", edited by Sir Henry Tidy, K.B.E., M.A., M.D. (Oxon.), F.R.C.P., and R. Milnes Walker, M.S. (Lond.), F.R.C.S.; Seventy-Third Year; 1955. Bristol: John Wright and Sons, Limited. 8½" x 5½", pp. 624, with many illustrations.

Follows the usual pattern of this publication.

"Principles and Practice of Antibiotic Therapy", by Henry Welch; in collaboration with Braley, Clark, Dowling, Finland, Herrell, Hinshaw, Hobby, Keefer, Knight, Pulaski, Rein, Ross, Smadel, Weinstein, Woodward and Zander; specially edited by Félix Martí-Ibáñez; 1954. New York: Medical Encyclopedia, Incorporated. New York and London: Interscience Publishers, Incorporated. 8½" x 5½", pp. 720. Price: $12.00.

Consists of three parts dealing respectively with the antibiotics, antibiotic therapy of infectious diseases, and antibiotic therapy in medical specialties. There are 26 chapters altogether.

The Medical Journal of Australia

SATURDAY, NOVEMBER 26, 1955.

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THE MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN.

THE report of the Medical Research Council of Great Britain for the year 1953-1954 has been published by the Committee of the Privy Council for Medical Research. It was presented by the Lord President of the Council to Parliament by command of Her Majesty in June, 1955. This report, which is a book of more than 250 pages, covers an enormous field—it not only gives an outline of the research programme carried out, but gives a list of establishments where work was done, with names of the scientific staff and summaries of the research. There is also a list of publications which covers 52 pages. During the financial year ended March 31, 1954, the total expenditure of public funds by the Council was £1,803,884 on ordinary account and £147,952 on non-recurrent account. In the previous year these two sums were respectively £1,726,687 and £240,421. The general expenditure, as is to be expected, continues to rise, for we read in the introduction that the provision by Parliament for the financial year 1954-1955 is £1,844,681 (including £50,000 for clinical research in the National Health Service); the provision for non-recurring expenditure for special apparatus and buildings is £102,428. It is interesting to note the way in which the grant-in-aid from Parliament is spent. The allocations in the year 1953-1954 were as follows: administration, 3·7%; general scientific purposes, 0·8%; National Institute for Medical Research, 19·4%; research units and groups and external staff, 55·7%; special schemes, 9·6%; temporary research grants and training awards, 10·6%; U.S. Conditional Aid Scheme, 0·2%. The Medical Research Council receives benefactions—by terms of its charter the Council is empowered to receive and administer such funds. During the twelve months under review it received two grants from America—$25,000 from the Rockefeller Foundation for travelling fellowships, and $16,000 from Eli Lilly and Company for the same purpose; a group of British tobacco manufacturers gave £35,715 for research in lung cancer; sums of £27,000, £7000 and £4595 have been given for research in blindness and deafness, coronary thrombosis and poliomyelitis respectively; several small bequests were received, and among the donations was one of $90,202 from an anonymous Canadian donor for general purposes of medical research.

It is clear that no useful purpose will be served by any attempt to set out the names or even the numbers of the establishments receiving grants from the Council, or the names of staffs and summaries of research—more than 50 pages of the report are occupied by this information. It is important, however, to insist, especially among those who have no intimate knowledge of research, whether they have had any training in medicine or not, that practically every conspicuous advance in knowledge depends on a mass of unspectacular work, all of which has been indispensable to the final result. Moreover, if the significance of the contributions made by different individuals and branches of science to the general progress of medicine are to be fairly appraised, it must be remembered "that all are not equally well placed to make those final contributions which attract public attention". To the non-medical person generalizations of this kind may not mean a great deal, though it may make him look with a less harsh eye at sums marked in the country's budget for research purposes. To the medically trained man these statements should carry a challenge. Not only should they make him look less coldly at unrelated observations made by persons of whom he has never heard and published by editors of whose discrimination he takes a poor view. They should show him that if he tries he may possibly find some link, some correlation, between what the "unknown" has written and what he has read at an earlier date. He may even be given a new start for observations of his own. But this is a digression.

The main part of the report includes some discussion of general trends in medical research. These discussions are eleven in number. They are written from a broader standpoint than that of the contribution made by the Council's own workers—this increases rather than lessens their interest. In the section on modern trends in chemotherapy the practitioner is reminded that chemotherapy has travelled a long way since the days when it amounted to little more than the empirical selection and biological testing of organic compounds, whether they were already known or were specially selected for the purpose. It is shown that biological research has invigorated the whole subject of chemotherapy. From bacterial biochemistry there is emerging "a satisfying theoretical background" for the work. "In the search for new synthetic chemotherapeutic drugs we may expect to be guided in general by this theory and in detail by increasing knowledge of the biochemistry of bacterial metabolism, and by the study of the mode of action of naturally occurring antibiotics." Drugs which may exercise their effects through the host

rather than directly on the parasite are now included among chemotherapeutic agents; the study of the cellular metabolism of higher animals has been of help in the development of this aspect of the subject. A plea is made for the cooperation of the chemist. "The task of the biologist and biochemist is to provide the clues for new advance; the intellectual approach and special skill of the chemist are required in order that these clues should be followed up with advantage." The section on blindness in premature infants contains a description of the investigation of retrolental fibroplasia by Norman Ashton at the Institute of Ophthalmology in London. The discovery that the effect of excessive oxygen on the premature eye is the main predisposing factor reads almost like a fairy tale. It need not be retold here. The restricted use of oxygen for premature infants has meant that retrolental fibroplasia has virtually disappeared as dramatically as it appeared a little over a decade ago. "Seldom has a disease, so apparently enigmatic in its causation, so intractable to treatment and so tragic in its effects, been so rapidly brought under control." The section on pernicious anæmia is a succinct account of the research in this condition since Minot and Murphy in 1926 discovered that it could be successfully treated by the administration of liver—Castle's conception of an extrinsic and an intrinsic factor whose absence from the gastric juice was responsible; the isolation of folic acid and the discovery of vitamin B_{12}; the contention of Castle that vitamin B_{12} must be regarded as identical with both the extrinsic factor and the anti-pernicious-anæmia principle of his original equation, the effect of the intrinsic factor being to promote the absorption of vitamin B_{12}; and the search for the exact nature and origin of the intrinsic factor and its attempted isolation. The section on trends in research in human malnutrition shows that the study of human malnutrition "is no longer the clear-cut investigation of disease entities"; it is the study of "the reactions of the individual throughout his life-span to what may be termed the chemical environment imposed by his diet". In regard to the neurotic in industry mention is made of some of the investigations by the Unit for Research in Occupational Adaptation, and it is pointed out that the practical problems facing the psychiatric investigator are numerous and not easily solved. The psychiatrist is on the horns of a dilemma. If his clinical, social and psychometric examination of each worker is to be adequate, it is impossible for him to examine a large population; but unless his examined population is large, his findings will be inconclusive. "He must examine his subjects during a comparatively short period, since economic changes in the industries studied may otherwise affect his results differently." One may ask, of course, whether it is sensible to make detailed studies in an industry in which such disturbing economic changes are likely to take place. The worker drawing conclusions from one investigation cannot feel confident that they will apply to different groups working under other conditions. The conclusion in the report is justified that surer and simpler methods of examination need to be devised before surveys of the kind described in the report can yield conclusions of general validity on the connexion between occupational behaviour and psychopathic traits.

Among the other subjects discussed in this part of the report are: "The Action of Biologically Active Substances on Tissue Cultures" and "Research on the Mechanism of Virus Infection". Any information on these subjects which is included is probably out of date by now. Sufficient has been included to show the range of the report. Attention should be drawn to one special point in conclusion. The Public Health Laboratory Service, which is directed by the Council for the Ministry of Health, has "regional laboratories", "area laboratories", "reference laboratories" and "special laboratories". There is a "Central Public Health Laboratory" in London. It must not be supposed that this service functions merely as an addendum to the National Health Service. It undertakes its own research programme and separate financial provision is made for it, by a vote of the Ministry of Health. During the year 1953-1954 the expenditure was £882,931 on ordinary account and £119,309 on non-recurrent account. The list of publications by members of the staff of this service covers four and a half pages.

Current Comment.

MICROBIAL INTERRELATIONSHIPS.

IT is only since the development of techniques for rearing germ-free guinea-pigs that accurate observations on the effects of symbiosis between associated organisms have become possible. Some paradoxical effects after the giving of certain drugs can be explained only as being due to an upsetting of the balance of the intestinal flora; for example, when certain antibiotics are included in the diet of a young guinea-pig most of the normal inhabitants of the intestines disappear, but some, unaffected by these antibiotics and relieved of the competition of, or freed from the restraint imposed by, the other inhabitants, multiply rapidly and finally kill the guinea-pig, although normally their presence in small numbers causes no damage. Another example is the occasional action of penicillin and sulphasuxidine, neither of which is amœbicidal, in clearing the bowel of amœbæ. It has also been shown that when *Entamœba histolytica* is grown *in vitro* with *Trypanosoma cruzi*, the pathogenicity of the amœbæ decreases, whereas with other associates, especially with a mixed bacterial flora, its pathogenicity becomes enhanced.

Recent experiments by B. P. Phillips and five of his colleagues[1] have produced some interesting results. They have shown that when germ-free guinea-pigs are inoculated with *E. histolytica* no lesions or symptoms follow, and the amœbæ die out within a few days; inoculation of normal guinea-pigs (in the sense of their having normal intestinal flora) with the same strain of *E. histolytica* is followed by typical manifestations of infection. But when germ-free guinea-pigs are inoculated with *E. histolytica* in association with either *Escherichia coli* or *Aerobacter aerogenes*, then typical infections develop; control animals, infected only with *E. coli* or *A. aerogenes*, develop no lesions.

That the associated organisms in some way facilitate the invasion of the mucosa by the amœbæ seems proved, even though the actual mechanism by which this is achieved has not been worked out. It is worth noting that the extent of invasion is less in the presence of one associated organism than it is in the presence of a normal, mixed intestinal flora; this suggests that other members of the intestinal flora may have their part in reinforcing the invasive action of the amœbæ, too. From this, it would seem reasonable to assume that penicillin, or sulphasuxidine, by destroying the facilitating organisms in the bowel, indirectly deprives the amœbæ of their invasive power. That this action occurs only sometimes could be explained

[1] *Am. J. Trop. Med. & Hyg.*, July, 1955.

by variations in the constitution of the intestinal flora and in its reaction to the drugs concerned. In these experiments, too, we find the explanation of why a combination of "Terramycin" and emetine acts so much more rapidly in the treatment of acute amœbic dysentery than either drug alone.

A secondary observation made during these experiments has some interest. The *T. cruzi* which accompanied the amœbæ did not produce any infection in the normal guinea-pigs, or when the associated *E. coli* or *A. aerobacter* were inoculated, but in the germ-free guinea-pigs *T. cruzi* could be found in their blood later. Add to this the fact that *Vibrio comma* produces infection in the germ-free as well as in the normal guinea-pig, and we have three modes of infection, for three varieties of organism. It is not unlikely that experiments on germ-free animals with other organisms will reveal further facts which may offer new light on the mechanisms of microbial symbiosis or antagonism. It is possible that the basis of the varying relationships between *E. histolytica* and certain of its associates depends on the excretion by the latter of substances which act as metabolites or antimetabolites in the substrate in which the organisms grow.

ENERGY EXPENDITURE AND FOOD INTAKE.

INCREASING INTEREST has been shown during the past few years in the importance of calorie expenditure and its relationship to dietary intake. Many studies have been made on different types of people and energy expenditure, but for a variety of reasons the results obtained did not give the information required. The latest of these studies has been undertaken by O. G. Edholm, J. G. Fletcher, E. M. Widdowson and R. A. McCance.[1] Twelve cadets in a military academy were studied for a period of two weeks. All belonged to the same unit and were selected as being similar in height, weight, athletic interests and training. All the food taken was weighed every day and allowance was made for plate and other waste. The calorie, protein, fat, carbohydrate and alcohol intakes were calculated from food tables. This is a weak point in the investigation. A careful diary was kept by each cadet noting as accurately as possible what was being done over a period of eighteen hours each day. Metabolic measurements were made on each subject by determination of oxygen consumption during the various activities. The mean expenditure of energy for the twelve cadets over the whole fortnight was very close to that of the intake, but in spite of the homogeneous nature of the groups and of their activities, the individual intakes varied by over 1000 Calories per day even when averaged over fourteen days.

It has always been a problem why two people of the same age and appearance and with similar occupations are so often found to have widely different calorie intakes. Differential change in weight is not the solution, and it has been thought that differences of intake must arise from differences in the expenditure of energy in doing the same things. This study has shown that men may expend remarkably different amounts of energy in performing the same task. If one man can walk, sit and lie with half to two-thirds the energy expenditure of another, he will clearly require to eat much less food. One person may need to eat much more food than another because his energy expenditure is much less efficient over all forms of expenditure. How quickly and closely need the supply conform to the demand when in any individual there is an increase in energy expenditure over any period? No correlation was found between the expenditure and intake of individuals on the same day, but there was a significant correlation between the mean daily expenditure and the mean daily intake two days later. It is difficult to explain this belated adjustment of intake of food to make correction for an expenditure of energy incurred days, weeks or months before; the same kind of thing takes place in persons who have had their food intake seriously restricted over a period and later have access to virtually unlimited food.

It is clear that one cannot be dogmatic about the amount of food an individual requires to carry on a certain kind and amount of activity, and a given diet may be more than adequate for one person and distinctly not adequate for another doing similar work under similar conditions.

[1] *Brit. J. Nutrition*, 1955, Volume IX, Number 3.

ESSENTIAL EFFECTS OF HYPOTHERMIA.

INTEREST in hypothermia has passed in recent years from the physiologists to the surgeons, especially the cardiac surgeons. This interest stems from the fact that reduction of body temperature results in reduced metabolic activity and lessened oxygen consumption. The cardiac surgeon, faced on the one hand with the natural desire to operate on a "dry" heart and on the other with the considerable difficulties of simultaneously maintaining an adequate circulation, hoped that here was a practical compromise. As was pointed out previously in these columns on June 5, 1954, the reduced oxygen requirement associated with reduced body temperature allows a much longer time during which intracardiac surgery can be performed, as the risk of permanent cerebral damage from arrest of the circulation is diminished. At the same time the amount of anæsthetic agents required is considerably less. This all sounds very well, but recent work reported from Johannesburg by Phyllis Knocker[1] indicates that too little attention has been paid to the effects on the body cells of the hypothermia. Knocker points out that though accepted opinion is that no gross alterations in tissue structure can be ascribed to the effects of refrigeration, it seems likely that delicate changes in the cell must take place; and, if demonstrable, these must give early warning of serious damage to come. With this in view a study was made in dogs of three vital organs, the liver, the kidney and the adrenal gland, to determine whether any histochemical changes could be demonstrated during hypothermia. After induction of anæsthesia, preliminary biopsy specimens were taken from the organs being studied. Hypothermia was then induced—being continued in the early experiments until death supervened, but subsequently to the point at which cardiac surgery is normally undertaken. Further biopsy specimens were then taken. The histopathological changes, which are illustrated in the article with a series of excellent colour photographs, are in summary as follows: accumulation of fat in the liver, kidney and adrenal glands; depletion of glycogen in the liver; vacuolation of the granular cells of the *zona reticularis* of the adrenal cortex.

The implications of these delicate histochemical changes, as Knocker states, may well be extensive. Accumulation of fat in the liver is always serious; it is associated with many abnormal states of the liver and must be accepted as a sign of damage to the hepatic cells. At the same time, the glycogen depletion increases the liability of the liver to injury. The available evidence is against attributing to anoxia the harmful effects of hypothermia on liver cells, but Knocker shows that the two states are attended by similar results; she suggests that, although oxygen may be readily available to the liver cells, hypothermia may in some way upset delicate enzyme systems, preventing the cells from utilizing the oxygen despite its ready availability. Her comment is illuminating:

> If this were true it would mean that the high venous oxygen content, characteristic of successful hypothermia, is due to an inability of the cells to utilise the oxygen rather than to their not requiring it. This would upset our whole concept of the effect of cold on cell metabolism; for, instead of reducing the oxygen requirements by cold, we should merely be paralysing some system which normally makes oxygen available to the cell. In our efforts then to prepare the organs for the insult of anoxia we should be using a technique which itself causes anoxia.

[1] *Lancet*, October 22, 1955.

The fat accumulation found in the adrenal cortex is a directly opposite finding from that of other workers, who have described depletion of fat—an accepted sign of Selye's "alarm reaction" to stress. Cold is undoubtedly a stress factor; so Knocker suggests that the altered response may be the result of the anæsthesia. Vacuolation of cortical cells was a constant finding in the present experiments, increasing with the prolongation and increase in cooling to the point of death; it thus appears to be "a serious omen". Knocker considers it likely that the increase in fat and the vacuolation are one and the same process.

The main renal changes consist in the accumulation of fat in the lower nephron—possibly the direct effect of cold on the tubules or the indirect effect of cold on the kidney, with shunting of the circulating blood and exclusion of the lower nephron. This would involve relative anoxia of the cells of the tubules. Knocker refers to the accepted role of cold in the production of nephritis and cites experimental work on rabbits in which cold injury produced both gross and microscopic renal changes. She points out that without survival experiments one cannot say that the changes described in the kidneys are irreversible. However, they do take place during hypothermia, and they undoubtedly represent pathological change.

Knocker draws attention to the similarity between the tissue changes induced by hypothermia and those described by Selye as bodily reactions to stress, and points out that we are driven to the conclusion that "contrary to our scientific expectations", hypothermia is at best an exposure to severe stress. The changes may not all be permanent, but they are pathological and may explain some deaths of laboratory animals undergoing cooling or subsequent rewarming. There is no proof that the changes are due to anoxia, but cellular anoxia can apparently lead to similar change.

This work from South Africa will undoubtedly provoke further inquiry into the clinical use of hypothermia. There has been a certain amount of uneasiness about it as the result of the findings of earlier workers, but the position has been vague and demands full reexamination, especially in relation to cardiac surgery. The aim of hypothermia has been to diminish the metabolism of the cells before temporary occlusion of the circulation. We must agree with Knocker that after seeing the tissue changes induced by the accepted degree of hypothermia, one questions whether the insult imposed upon the tissues by cold is sound preparation for ensuing anoxia.

PHYSIOLOGICAL VOICE PRODUCTION.

A FAIRLY recent phenomenon in popular entertainment is the vocal style exhibited by Negro singers, especially Negro women, in which unusual effects are created by using the chest register to sing higher tones which, by all traditional European standards, should be sung only by means of the middle register. Esti D. Freud[1] analyses this singing style and uses it as a starting point for a discussion on the physiology of singing. Freud reminds us that the most preferred singing in Europe used to be that of male sopranos, castrated before puberty, and that up until the end of the eighteenth century most female operatic roles were written for *castrati*; the last important male soprano, Domenico Mustapha, died as recently as 1912. As castration came to be rejected as unnatural and inhumane, the nearest natural substitute for *castrati* voices, *bel canto*, sung by tenors and women, was developed. Commencing with Wagner's operas, modern music has become largely impossible for *bel canto*, but the basic European tradition remains, and women singers normally use their three registers within the traditional limits.

However, Negro women, when they follow the traditional Negro style of singing, seem to have no difficulty in extending their chest register to compass very much higher notes. Questions that arise are whether this is the "natural" style, and whether the European style, based on *bel canto* and derived ultimately from the *castrati*, is not actually "artificial". It might be assumed, on the face of it, that Negroes would be likely to develop a natural style—but then what of the falsetto nasalization of the Chinese, and other possibly "natural" styles? On the other hand, white women singers, much as they might wish to sing, with their chest register, beyond the F above middle C, can rarely accomplish this, and almost never do so for any length of time without causing considerable damage. Freud describes how many white women entertainers, in imitation of Negro women singers, or in meeting their competition, strain to reach higher notes with the vocal cords well abducted and unshortened; the result is usually that they completely lose the ability to use their middle register, and then their speaking voice drops, even by five or six tones, becoming husky and losing much of its resonance. Eventually, all singing and speaking become painful, and medical attention becomes necessary. This does not seem to happen to Negroes—whether because they never attempt any use of the middle register, whereas white entertainers must attempt both styles concurrently in earning their living, or else because there may be some differences in larynx, vocal cords and nasal cavities in Negro women which facilitate extended use of the chest register, Freud does not offer an opinion. But, since the orthodox style produces the best singing without causing disturbances, she concludes that the traditional European style of singing most closely approaches the physiological method of voice production.

[1] *Arch Otolaryng.*, July, 1955.

THE USE OF COBALT IN THE THERAPY OF ANÆMIA.

IT has been known for some time that the administration of small doses of cobalt salts induces erythrocytosis and, if in sufficient dosage, polycythæmia. The mode of action of the cobalt is not known, but there is evidence that it is a toxic effect in the bone marrow causing anoxæmia, a known stimulant to red cell formation. The effect has, apparently, nothing to do with vitamin B_{12}. There is considerable evidence that in the anæmia of chronic infection and of chronic nephritis with uræmia small doses of cobalt give good results, but here it is doubtful whether the results are lasting. Recently iron preparations containing small amounts of cobalt for the treatment of the common types of anæmia have appeared on the market. As there was some doubt as to the therapeutic value of cobalt with iron as against plain iron preparations in such anæmias, the editor of *Blood* requested answers to three questions from seventeen members of his editorial board; all were interested in blood diseases.[1] The opinions of the members on the following points were requested. (*a*) The use of cobalt preparations in the treatment of anæmias. (*b*) The use of cobalt to "potentiate" iron therapy in the treatment of iron deficiency anæmia. (*c*) The value of certain cobalt-iron preparations. Almost all the members of the editorial board stated that cobalt administration might cause a rise in red cell and hæmoglobin levels of patients with anæmia due to renal insufficiency, but most of these did not believe that the effect was lasting or really valuable. Most considered it to have no value in other types of anæmia. Many drew attention to toxic effects which could be troublesome, such as nausea, severe *angina pectoris* and claudication of leg muscles. Nearly all agreed that there was not sufficient evidence at present to say whether cobalt potentiated iron therapy, but most considered that it did not or that the toxic effects of the cobalt overshadowed any useful effects. Since response to iron in straightforward deficiency states is so satisfactory, there is no need for the addition of cobalt. All agreed that the administration of preparations of iron and cobalt was not justified on present evidence.

[1] *Blood*, August, 1955.

The editor of the journal sums up the answers as follows:

> It seems well-nigh unanimous from the above comments that cobalt has little if any value in the clinical management of anemia. Even in the anemia of chronic nephritis for which some beneficial results have been claimed, although there may be a slight improvement in red cell values, there is probably little if any clinical benefit for the patient. Our experience with cobalt in the treatment of hypoplastic anemia and other instances of bone marrow failure has been almost uniformly disappointing. In iron deficiency, there seems little if any indication for using anything other than iron, which has such striking value. Because of the almost complete unanimity of the panel in this regard and because of the possible toxicity of cobalt in some patients, it seems unwise to recommend either cobalt alone or cobalt with iron to the medical profession.

Another aspect of this question is the addition of cobalt in amounts which might be toxic to some people to the much advertised shotgun mixtures of vitamins and mineral salts. The most recent studies on iron and cobalt metabolism are presented in a paper by R. G. Holly.[1] He made observations on 78 pregnant women, 58 of whom received cobalt and iron and 20 received cobalt alone. Iron alone was given to 94 patients and 55 received neither iron nor cobalt. In the control group there was a decrease in the mean hæmoglobin level and the hæmatocrit reading associated with decreased serum iron content. A supplement of iron or iron and cobalt prevented these reductions. The cobalt supplement did not prevent the decreases. The author claims that the addition of cobalt to the iron gave slightly better results than the iron alone. The figures given in the paper do not justify such a claim, as the differences are small and there is no statistical evaluation. The author claims that there were no toxic manifestations following the ingestion of cobalt, but he does mention skin rashes and gastro-intestinal intolerance. It has been claimed that cobalt administration causes histological changes in the thyroid. The author states that in his experience the administration of cobalt or cobalt and iron to mice, rats and pregnant women did not result in goitre formation. C. H. Jaimet and H. G. Thode studied the effects of cobalt therapy on thyroid function in children.[2] They found that the administration of one, two, four and six milligrammes of cobaltous chloride per kilogram of body weight for ten weeks caused no significant change in thyroid function in 17 children. No thyroid enlargement was seen in any of the cases and the radioactive iodine tests gave normal results.

EFFECTS OF THE ADMINISTRATION OF HYDROCORTISONE.

NEW REMEDIES sometimes have unexpected side effects which are not suspected until a certain amount of damage has been unwittingly done. In recent reports, L. L. Sparks and four associates[3] describe how, in mice, the administration of hydrocortisone caused calcification in the heart muscle. The mice were being used in experiments to determine the effect of hydrocortisone on transplantable mammary carcinoma—incidentally, it was shown that it inhibits the growth of the tumours, but shortens the survival time of the mice. The mice, two to three months old, received, by injection, 0·2 milligramme of hydrocortisone acetate daily for two weeks, then 1·0 milligramme daily for three weeks, and finally 0·5 milligramme daily. Those which survived for thirty days or more had grossly visible calcific deposits in their heart muscle; the amount of calcium deposited was roughly proportional to the duration of the injection period. Microscopic examination of the myocardium showed extensive calcification and degeneration of the muscle fibres; the nuclei showed some variation in size and shape; and granular, basophilic deposits of varying size were spread throughout the myocardium of the ventricles and the interventricular septum. There were small deposits of calcium actually within the muscle fibres. No such lesions were seen in the control animals, who received no hydrocortisone.

Further studies, in both tumour-bearing and normal mice, produced similar results. Adrenocorticotrophic hormone produced similar results. When growth hormone was injected simultaneously there seemed to be some potentiation of the calcification, whereas prolactin prevented it.

In the same issue of *Nature*, A. Lostroh and C. H. Li (the latter having been one of the associates in the first work) report that the above results have been confirmed spectrophotometrically, and that the amount of calcium deposited varies directly with the amount of hydrocortisone administered. Calcium deposits were heaviest in the walls of the right ventricle; some also appeared in the liver and other viscera.

Although the doses of hydrocortisone given to these mice are relatively higher than would normally be given to human beings, and although it is wrong to extrapolate results from one species of animal to another, totally different, there is nevertheless food for much thought in these reports. It can certainly be said that in the event of any human patient's dying after having been treated with hydrocortisone or related steroids, a careful search for evidence of calcium deposition is called for.

[1] *J.A.M.A.*, August 13, 1955.

[2] *Ibidem.*

[3] *Nature*, September 10, 1955.

AN EMULSIFYING AGENT IN DIGESTIVE DISORDERS.

ACTUAL or relative deficiencies of digestive enzymes, as in sprue and chronic pancreatitis, or in short-circuiting of the bowel, with steatorrhœa, lead to abdominal discomfort and nutritional deficiencies. High-caloric feeding is used to combat these deficiencies, but patients with these conditions are precisely those who have considerable distress from forced feeding, and any means of increasing absorption of fats and thereby reducing the amount of extra foods to be ingested are very welcome. E. Murray Burns[1] has reported on the use of commercial emulsifying agents for this purpose. Emulsifying agents are used in paints, cosmetics, insecticides and certain food products; they are combinations of hydrophilic and lipophilic fractions, which tend to congregate at the water-oil interfaces and penetrate between the molecules, ultimately producing finely divided emulsions, either of oil in water or water in oil, depending on their composition. In the intestine a suitable emulsifying agent can break down fat particles into minute droplets which more easily reach the villi and are more easily absorbed. When esters of fatty acids are combined with polyoxyethylenes such agents result. One of these, polyoxyethylene sorbitan monooleate ("Tween 80" or "PSM"), is non-toxic to man, and has a very strong emulsifying effect on fats in the intestine. Burns has used this substance, in doses of one to two grammes three times a day for adults, or 40 milligrammes for each gramme of ingested fat, in cases of sprue, chronic pancreatitis, resection of the small bowel, gastrectomy, and cholecystectomy; he reports that in some instances digestive disturbances and diarrhœa are reduced, the amounts of fat found in the stools are correspondingly less, and absorption of vitamin *A* (and presumably of other fat-soluble vitamins) is increased. Burns does not recommend the use of this emulsifying agent as routine treatment in all such cases, but he does suggest, with reason, that it can often be employed with benefit.

[1] *Northwest Med.*, September, 1955.

Abstracts from Medical Literature.

MEDICINE.

Chronic Auricular Flutter.

J. B. HOFFMAN and M. POMERANCE (*Ann. Int. Med.*, April, 1955) review the literature on chronic auricular flutter and report seven cases of their own. They point out that the diagnosis even with the help of the electrocardiogram is often difficult. Likewise the treatment is unsatisfactory, for a high proportion of patients do not revert to normal rhythm after treatment with digitalis and quinidine.

Hirsutism and Juvenile Hypothyroidism.

W. H. PERLOFF (*J.A.M.A.*, February 19, 1955) describes four children with hirsutism involving the back, shoulders, outer aspects of arms and legs and to a lesser degree the sides of the face, as well as having other evidence of hypothyroidism. They were relieved or cured of the hirsutism after six to eight months' therapy with desiccated thyroid.

Psittacosis.

R. H. FITZ, G. MEIKLEJOHN and M. D. BAUM (*Am. J.M.Sc.*, March, 1955) report an increasing incidence of psittacosis in the United States. The majority of their patients appear to contract the disease through parrakeets. Treatment with penicillin has been relatively ineffective, while treatment with chlortetracycline, oxytetracycline or tetracycline has been usually followed by prompt improvement.

Telescoped Urinary Sediment.

G. E. SCHREINER (*Ann. Int. Med.*, April, 1955) presents three cases of chronic glomerulonephritis confirmed at autopsy in which the urine contained elements characteristically found in the three stages of acute nephritis. This telescoped sediment is therefore not confined to patients with visceral angiitis.

The Transmission of Infectious Mononucleosis.

R. J. HOGLAND (*Am. J. M. Sc.*, March, 1955) reviews the available evidence on the transmission of infectious mononucleosis. The hypothesis is proposed that mononucleosis is transmitted chiefly by direct intimate oral contact which allows for salivary exchange, and that the incubation period of the disease is about thirty-three to forty-nine days. The hypothesis explains the unusual age incidence, the increased seasonal incidence in collegians, the fruitless results of attempts at experimental transmission, and the absence of transmission to room and ward mates.

Cerebro-Spinal Fluid in Tuberculous Meningitis.

H. W. GIERSON and J. I. MARX (*Ann. Int. Med.*, April, 1955) have correlated the cerebro-spinal fluid sugar and chloride content with the diagnosis and prognosis in 231 cases of tuberculous meningitis. Both chloride and sugar contents were low in most instances, but in a significant number of cases one or the other was normal at the time of initial examination and remained so throughout the diagnostic period. The authors state that the level of neither glucose nor chloride provides a sensitive prognostic index. In diagnosis and prognosis depression of chloride level is a more reliable sign than depression of glucose level.

Infectious Hepatitis.

G. REWERTS (*Deutsche med. Wchnschr.*, 1955, No. 2, page 82) writes on the epidemiological and clinical aspects of infectious hepatitis. He quotes the observations of Beckmann *et alii* that epidemic viral hepatitis is often followed by bacterial cholecystitis, cholangitis or cholangiolitis; he also refers to the observations of Kalk *et alii* concerning a "polytropism" of the virus of infective hepatitis. He has confirmed these observations in 13 cases. Two families were infected. Seven patients had a lesion of the liver cells, two manifested gastro-enteritis only, whereas six patients after a period of mild gastro-enteritis presented symptoms of cholecystitis, cholangitis or cholangiolitis. The author points out that hepatitis may masquerade as abortive gastro-enteritis or cholecystitis and hence may remain unrecognized. It thus follows that the spread of infective hepatitis cannot be stopped simply by isolation of the "true" hepatic infections.

Stress and Gastric Secretion in Peptic Ulcer.

H. SHAY AND D. C. H. SUN (*Am. J. M. Sc.*, December, 1954) produce experimental evidence in man that the stress effect of insulin hypoglycæmia acting on the posterior part of the hypothalamus initiates reactions that result in increased gastric acid secretion and that intact suprarenal glands are necessary for this purpose. Their evidence suggests that adrenaline is liberated in the stress effect of insulin hypoglycæmia and plays an important part in the cycle that results in the stimulation of gastric secretion. They believe that it will be necessary to consider a suprarenal phase of gastric secretion in the study of peptic ulcer and that such a phase is a significant part of the harmful somatic mechanisms activated by stress reactions.

Ferric Iron in Marrow Cells.

W. I. MORSE (*Canad. M.A.J.*, March 15, 1955) discusses stainable ferric iron particles in erythroid marrow cells and erythrocytes. He states that small particles of non-hæmoglobin iron, stainable with potassium ferrocyanide and hydrochloric acid, appear in the erythrocytes in acquired hæmolytic anæmia after splenectomy, and in lead poisoning. These cells are called siderocytes. Iron particles also appear in the normoblasts of bone marrow (sideroblasts). It is suggested that the intact spleen removes siderocytes (iron-containing cells) from the blood selectively. This is supported by evidence that splenectomy lessens the anæmia of lead poisoning, and idiopathic hæmolytic anæmia with a high sideroblast count. Sideroblasts are present in normal marrow aspirates, and iron deficiency is indicated when less than 15% of normoblasts show stainable iron particles. High counts were obtained in thalassæmia and lead poisoning. The affected normoblasts are present in large numbers in pernicious and related megaloblastic anæmias, in thalassæmia and in idiopathic erythræmic myelosis.

Peptic Ulcers and ACTH.

B. I. HIRSCHOWITZ *et alii* (*J.A.M.A.*, May 7, 1955) discuss the role of gastric secretions in activation of peptic ulcers by ACTH. Investigations showed that ACTH produced in normal subjects an increase in hydrochloric acid and pepsin and a reduction in the viscosity and content of visible mucus of the gastric juice. Urinary excretion of pepsinogen was increased by ACTH. In a duodenal ulcer subject, exacerbation of the ulcer occurred after four days' ACTH administration, though there was no abnormal rise in the amount of gastric acid or pepsin or of urinary pepsinogen. Reduction of viscosity and of visible mucus preceded the exacerbation of the ulcer and may have played a part.

Reserpine.

E. L. REA AND J. F. FAZEKAS (*Arch. Int. Med.*, April, 1955) discuss the effects of parenterally administered reserpine. Four to 15 milligrammes of reserpine were given intravenously to agitated patients, one with *delirium tremens* and another an agitated patient aged sixty years, and to four patients with psychomotor agitation resulting from acute alcoholism. Orthostatic hypotension was noted; generalized flushing of the skin and respiratory distress occurred. The authors state that the results were not satisfactory, and the administration of reserpine did not seem advisable in the treatment of acutely disturbed alcoholics.

Carotid Angiography.

D. PARKINSON AND A. E. CHILDE (*Canad. M.A.J.*, April 15, 1955) present a clinical evaluation of 200 consecutive cases in which carotid angiography was performed. The patients varied in age from two months to eighty years. The technique of this procedure is described, and the indications for it are given. The authors state that, with due care and skill, cerebral angiography is an extremely valuable diagnostic procedure associated with comparatively little risk. Its overall diagnostic value does not equal that of cerebral pneumography, but it should be used more frequently as a primary procedure in cases of suspected brain tumour and also as a routine for suspected vascular anomalies in properly selected cases.

The Treatment of Trichomonas, Monilia and Mixed Infections of the Vagina.

A. SANCIER AND R. SIMARD (*Canad. M.A.J.*, April 15, 1955) describe the treatment of trichomonas, monilia, and mixed infections of the vagina with "Propi-Vaginal", which is a vaginal suppository containing sodium propionate, propionic acid and diiodohydroxyquinoline, with added lactose, dextrose, boric acid and lactic acid. Treatment with three of the suppositories daily for three days, then two daily for twelve days, and thereafter one per day

for a period of fifteen days, was found to lead to complete cure in approximately 80% of cases, without any evidence of local irritation due to the presence of the suppositories. Results were checked by repetitive vaginal smear examinations.

Recent Studies in the Diagnosis of Cat Scratch Fever.

S. S. KALTER, J. E. PRIER AND J. T. PRIOR (*Ann. Int. Med.*, March, 1955) discuss recent studies on the diagnosis of cat scratch fever. They state that this clinical syndrome is referred to as non-bacterial regional lymphadenitis or benign inoculation lymphoreticulosis, and is being recognized more frequently. Because the combination of lymphadenopathy and low-grade fever can mimic so many disease processes, the authors' chief interest in this entity has been centred about an evaluation of the laboratory methods currently considered to be of value in the diagnosis of cat scratch fever. The protean nature of the complaint often leads to confusion in its diagnosis. The present report places emphasis on the skin test and serological determinations. This study describes the clinical variation as seen in more than 250 cases. The histopathology, as based on the microscopic study of lymph-node tissue from between 30 and 40 definitely proved cases of cat scratch fever, is described. Many people are apparently scratched by cats, or are at least intimately associated with them, and fail to react to skin tests. It appears that not all cats are carriers of the agent (or agents) causing this syndrome. The cats also appear to be physically healthy, and complete necropsy studies of several of these animals failed to reveal significant abnormalities. Several cats have been studied in an attempt to isolate an ætiological agent, but without success. The skin test with the use of an antigen prepared from materials obtained from lymph nodes of patients with the disease appears to be the best available diagnostic procedure at present. This conclusion is based on the results of skin-test studies on a large number of subjects of cat scratch disease and on normal controls. The serological examination and the histopathology of the biopsy specimen (lymph node), although suggestive, can in no way be considered specific. In the presence of a history of contact with cats, especially of a cat scratch, and positive skin test result, biopsy of an affected enlarged lymph node is not considered essential for the establishment of the diagnosis of cat scratch fever. The ætiology of this disease remains obscure, as does its relationship to the *lymphogranuloma venereum* - psittacosis group. The need for caution is emphasized in the use of antigenic material for skin testing from patients with a history of jaundice.

Gold-Hormonal Therapy in Rheumatoid Arthritis.

P. J. BILKA AND M. H. WEIL (*Ann. Int. Med.*, March, 1955) present a review of the literature on gold-hormonal therapy in rheumatoid arthritis. In addition an evaluation is made of the results of treatment of 50 patients with rheumatoid arthritis who were given combined gold and hormone therapy. They were given combinations of gold and cortisone, hydrocortisone or corticotropin. The maximum dosage of gold was 50 milligrammes of the salt used once a week. Forty-one patients tolerated a minimum total dosage of 500 milligrammes of gold salt, and were observed for at least three months. Of the patients 17% maintained a complete remission of their disease; 39% showed major improvement; 12% showed moderate improvement; 32% maintained little or no improvement on gold therapy after the hormone was stopped. These results closely approximate to those obtained by the use of gold alone. The incidence of gold reactions was 46%, and in 36% of cases gold therapy was discontinued because of toxicity. Hormone therapy does not lessen the need for the usual precautions when gold salts are used. Combined therapy offers a practical means of treating the patient with severe active rheumatoid arthritis. Cortisone, hydrocortisone or corticotropin can be used to suppress the disease for several weeks to months while the gold depot is being built up. The hormone can then be discontinued, with the expectation that the same therapeutic result will be obtained as if gold alone was administered. Patients not showing a favourable response to the combined programme can be treated by long-term maintenance on small doses of hormone, or by an intensification of the usual conservative measures of established value, in the case of the patient with rheumatoid arthritis. The authors conclude that hormone therapy neither potentiates nor inhibits the effectiveness of gold.

Thyroid Carcinoma.

S. KRAMER, H. P. CONCANNON, H. D. EVANS AND G. M. CLARKE (*Brit. J. Radiol., June, 1955*) report on 48 cases of carcinoma of the thyroid which have been investigated with radioiodine at the Royal Cancer Hospital, London. A tracer study was performed on each patient, and the thyroid and regions where metastases were suspected were scanned; and in recent years, scanning of the whole body was carried out in an attempt to discover uptake in any clinically unsuspected metastases. The amount of radioiodine retained in the body and the amount excreted in the urine were measured. The patients could be separated into three groups. In the first group there was no evidence of uptake in the body, and most of the isotope was excreted in the urine; these were treated by surgery or external irradiation. In the second group uptake in the tumour was masked by normally functioning thyroid tissue in the neck; here the thyroid was ablated by surgery or radiotherapy, further tracer studies being carried out later, and in some cases an attempt was made to enhance the uptake in tumour tissue by a course of thiouracil. In the third group the uptake in tumour tissue was enough to warrant immediate therapy with radioiodine. Of 13 patients who had some iodine uptake in the tumour, 12 were treated with radioactive iodine. The initial therapeutic amount was usually 100 to 150 millicuries. Five patients showed evidence of improvement, one patient with widespread pulmonary metastases being alive and well and clinically free of disease five years after therapy. Iodine studies have been successful in demonstrating some metastatic deposits previously undetected by routine clinical methods. The authors state that the review confirms the general experience that relatively few patients with thyroid carcinoma can as yet be successfully treated with radioactive iodine.

Manganese Poisoning in Moroccan Miners.

J. RODIER (*Brit. J. Indust. Med.*, January, 1955) surveys recent knowledge of manganese poisoning in Moroccan miners. After a brief introduction on the manganese deposits where the disease is encountered, the clinical syndrome is described. One hundred and fifty cases of poisoning have provided the material for these investigations. Manganism is studied under its two aspects: the neurological syndrome progressing inexorably and irreversibly, and the pneumopathies. Individual susceptibility, whose role seems important in this condition, and the conditions for toxicity are successively discussed. The latter constitute one of the most difficult problems, since prophylaxis depends directly upon it. Some problems, such as the part played by dust, are described. The author states that if at present treatment of the disease is only palliative and cannot produce regression of symptoms, the elimination of manganese by the use of calcium versenate opens new possibilities. An important section is devoted to problems of prophylaxis, and exact indications are given of both medical and technical measures to be taken. Finally certain legal aspects of compensation are presented and discussed. The author has included clear concise tables and explanatory photographs illustrating the main clinical features of manganese poisoning.

Gastro-Œsophageal Incompetence, Partial Intrathoracic Stomach and Vomiting in Infancy.

F. N. SILVERMAN (*Radiology*, May, 1955) states that the identification of the cardio-œsophageal junction by any single technique is subject to considerable error. Clear differentiation between "chalasia" and partial thoracic stomach is not always possible. In fact, the similarity in manifestations, complications and response to therapy is such as to suggest that the two conditions may be identical, if not different stages of the same condition. Conclusive diagnosis probably is not warranted in either instance unless the free reflux from the stomach into the œsophagus can be demonstrated to occur whenever it is sought for; production of reflux by positioning and pressure is less satisfactory than spontaneous reflux for identifying a primary abnormality in the region of the cardio-œsophageal orifice in a child who is vomiting. "Congenital short œsophagus" probably does not exist as an entity but represents the effect of regurgitation of acid gastric contents into the œsophagus—namely, œsophagitis and cicatricial retraction of the organ or its mucosa. Postural treatment is the method of choice when gastro-œsophageal insufficiency is observed in early infancy.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on June 30, 1955, at the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney, DR. H. H. WILLIS, the President, in the chair.

The Uses and Abuses of Blood Transfusion.

DR. K. J. B. FAGAN read a paper entitled "The Use and Abuse of Blood Transfusions" (see page 881).

DR. I. S. COLLINS read a paper entitled "The Uses and Abuses of Blood Transfusion" (see page 883).

DR. C. N. PATON, in opening the discussion, said that he spoke as one who had begun giving blood transfusions when the procedure was to type the blood of the patient's friends, and then set about taking blood from the most likely one into a bottle of citrate solution. After that the blood was given to the patient. That was a long and hazardous proceeding. From that state of affairs they progressed to the Toc H Donors' Club, where there were numerous donors whose blood was already typed and arranged in groups. The club would be rung up and told that two donors of a particular group were needed as quickly as they could be sent, and the donors were sent along very quickly. That meant a saving of time. The patient's medical attendant took the blood from the donors, and then proceeded to give it to the patient. Nowadays the supplying of blood had become merely the matter of a telephone message to the Red Cross Blood Transfusion Service, which gave a first-class service. Dr. Paton expressed the deep appreciation of himself and of all anæsthetists, who had much to do with blood transfusion, of the excellent service given. Anæsthetists realized that the Service had difficulties to surmount, and they tried to cooperate to the best of their ability. They tried especially to reduce the unnecessary consumption of blood; Dr. Paton thought that there was a good deal of opportunity for that reduction. He agreed with almost all that Dr. Fagan and Dr. Collins had said.

Dr. Paton said that he had been struck by Dr. Fagan's remarks about the measuring of the quantity of blood according to the number of millimetres of mercury by which the systolic blood pressure had fallen. Dr. Paton thought that that method originated from the American flair for measuring everything. Australian anæsthetists used their clinical sense more than any yardstick of measuring to gauge the amount of blood required. After many years' experience one developed a second sense, by which one could tell at once by the patient's colour, by the feel of the skin, and by the volume of the pulse and its rate, whether blood was needed and approximately how much. Dr. Paton found that in later years he was relying more and more on that sense. He gathered the impression that Dr. Fagan was strongly of the opinion that blood was the essential thing in the treatment of shock. Dr. Paton said that a great deal of blood was consumed in the treatment of shock of various kinds. When shock was hæmorrhagic in nature, undoubtedly blood transfusion was the treatment *par excellence*; but there were other degrees of shock in surgical practice that were not due to blood loss. Dr. Paton suggested that such things as prolonged pulling on the kidney entailed a good deal of traumatic shock, which, as it was of a temporary nature, could be combated by the exhibition of the well-known plasma expanders. They were expensive, but good, in spite of what people said about the size of their molecule and the length of time it took to excrete them. Clinically they answered the purpose well. They could also be used as a substitute for blood. Dr. Paton mentioned their use during the performance of a Wertheim operation. Because the patient's blood was of a rare type, it had been possible to secure only two bottles of blood. The operation lasted some three hours, and it was completed with the use of two half-litres of "Dextraven" as a plasma expander; no doubt, had it been possible to secure four bottles of blood, they would have been used.

With regard to the preparation of patients for operation by blood transfusion, Dr. Paton said that great emphasis had been laid on the use of packed cells. No doubt in hospital practice that was the ideal course; but he found that because of the itinerant form of practice which most anæsthetists pursued, certain difficulties were met with in their hospital-to-hospital progress. It was common knowledge that packed cells could not be preserved, but had to be used on the day on which they were withdrawn from the donors. It was not always convenient for the anæsthetist to be on the spot to instal the transfusion apparatus and get it going at the right time. Secondly, a packed red cell transfusion presented certain difficulties not associated with the ordinary whole blood transfusion. The substance was thick and viscid and apt to cause blockages, and needed much expert supervision to keep the transfusion going. Therefore, in the itinerant form of practice described one was apt to avoid packed cell transfusions. Dr. Paton said that he avoided using them as much as possible away from public hospitals of whose honorary medical staffs he was a member. The object of packed cell transfusions was to raise the hæmoglobin value to a level which made anæsthesia and surgery safe; they did this satisfactorily, and apart from the inconvenience of giving them they were ideal. By the giving of whole blood many more benefits were conferred on the patient than simply the raising of the hæmoglobin value. For example, depletion of serum and plasma proteins was adequately dealt with by the exhibition of whole blood; certain mineral constituents were also contributed by whole blood. Much of that benefit was lost by the giving of packed cells.

Dr. Paton said that he had been glad to hear Dr. Fagan say that transfusions should never be used to redeem the defects of surgical workmanship. With all due respect to surgeons, Dr. Paton thought that was becoming a habit; because blood was easily obtainable, surgeons were apt to think that it did not matter if the patient lost some. That was a wrong attitude; if the patient's blood did not matter, the blood wasted mattered to the donors. Furthermore, he did not agree at all with the setting up of transfusions for operations just because it was a routine practice. He had seen transfusions installed for the performance of a radical mastectomy before the operation had even begun. He regarded that as a reflection on the surgeon's ability for one thing, and for another as a capricious and vexatious wasting of the donors' blood. He thought that transfusions should not be given until the indications that they were needed arose. He also thought that it should be pointed out to the Red Cross Blood Transfusion Service that there the anæsthetist was up against something of a difficulty. He was not always able to anticipate the requirements for blood, and in his eagerness to be forearmed as well as forewarned he was apt to order blood that might not be used at the time. He was then left with certain unused bottles of blood, and he was obliged to return them to the depot forthwith. That could not always be done by a busy doctor. Dr. Paton thought that some arrangement could easily be made by which such bottles could be returned to the nearest public hospital. Blood could be saved in that way. Dr. Fagan had pointed out that the routine treatment of burns differed in different hospitals. Some people concentrated on using serum, protein or plasma, others gave whole blood. In any case, transfusion was a great boon in the treatment of burns throughout the long convalescent period with its exhaustion, anæmia and other indications for blood. With regard to arterial transfusions, Dr. Paton said that he had never seen one patient who he considered had benefited from it. He had seen the circulation of the hand severely threatened, although not completely destroyed. On the occasions on which he had seen an arterial transfusion given, it had been a last resort and had not produced beneficial results. The idea behind it was that the coronary circulation was at once improved, and the volume of circulating blood was thereby enhanced. However, it had recently been shown by experimental work on dogs that massive intravenous transfusions under pressure brought about as rapid and as satisfactory improvement from hæmorrhagic shock as did arterial transfusions. Thus, not much was gained by giving a transfusion through an artery, and a good deal of extra risk was run.

With regard to the risks of blood transfusion, Dr. Paton said that pyrogenic reactions had been mentioned by both speakers, and he thought that they presented a real risk. They were in his opinion much more common than was thought, and particularly so in the small private hospitals in which most of the work was done. A good deal of improvement was needed in the care of giving sets. He found that the sets offered to him at most of the private hospitals were "not fit for human consumption"; they were encrusted with the remains of the blood from the last transfusion, the rubber parts were in a state of decay, the needles were blunt; nothing so impeded the giving of blood as the use of an old, worn-out transfusion set. A lot was due to ignorance; many of the theatre sisters and nurses in charge of the setting up did not know the way to prepare a set, and it would be an advantage if they took to heart the instructions of the Red Cross Blood Transfusion Service on the subject. Dr. Paton said that for those reasons he took with him his own sets, and spent considerable trouble and

hard work in preparing them. He put all the glass tubes through a chromic acid bath, and went carefully through the rubber parts, discarding those that were worn, creased or discoloured. He had found that rubber tubes would last only through four to six autoclavings; his impression was that hospitals tried to make them last through 46. Dr. Paton thought that the risk of air embolism was largely over-emphasized. He had seen considerably more than 30 cubic centimetres of air pass into a vein through a transfusion tube on quite a number of occasions, with no evidence of embolism. However, he agreed with Dr. Fagan that a transfusion given under pressure did mean an added risk of the intake of large quantities of air. Circulatory overload also he thought was greatly over-emphasized; he could not recollect ever seeing it happen. He had seen a patient develop a few moist signs at the bases of his lungs; but he could recollect people who had received as much as 80 bottles of blood with no sign of circulatory overload. In a patient with severe cardio-vascular disease, and a seriously embarrassed left ventricle, perhaps, overload might be anticipated, but certainly not in a healthy patient.

With regard to over-transfusion, Dr. Paton said that another risk lay in wait for the transfusionist. It had struck him on numerous occasions that when a patient had received many bottles of blood and was then submitted to operation, everything bled. Only the previous week he had anæsthetized for the reopening of her abdomen for hæmostasis, late in the afternoon, a woman who had undergone hysterectomy in the morning. A ligature had slipped off the ovarian ligament. She had received nine bottles of blood before being taken to the operating theatre, and Dr. Paton was struck by the fact that the stitch holes in the skin wound bled when the sutures were removed; the superficial fascia and the muscles were an oozing mass. In fact, everything was oozing, including the pedicle which was responsible for the whole debacle. Dr. Paton had noticed a similar occurrence on a number of occasions associated with surgical catastrophes, and it had struck him that perhaps they were pouring in too many anticoagulants—that they were transfusing blood that contained quite a lot of sodium citrate and citric acid at a rate far faster than it could possibly be metabolized and assimilated. Probably, if they did that, they were defeating the very object that they were seeking; they were setting out to achieve hæmostasis and blood replacement, and they were pouring in much material that acted as an anticoagulant. Dr. Paton wondered whether others had had the same experience. The over-freezing mentioned by Dr. Collins contained yet another risk, and Dr. Paton thought it accounted for the wasting of a good deal of blood. The nurse, in an effort to be scrupulously careful, always put the blood close to the freezing coils, where the temperature fell considerably below zero. Dr. Paton thought that when that was done, the most fragile type of cell was the leucocyte. The corpuscular bodies collapsed, and a glairy white-of-egg-like precipitate was formed in the bottom of the bottle. Later the bottle of blood was taken from the refrigerator and inverted for administration, and the white-of-egg-like substance got down among the gauze filter, which very shortly became almost impermeable. The experience usually was that a third or fourth of the bottle of blood ran through, and then the transfusion began to slow up and soon came to a stop. That was the result entirely of over-freezing; it should be impressed on everyone that blood should not be placed near the coil in a refrigerator, but should be put in the most remote corner, where the temperature could be maintained at the necessary level.

Referring to accidents due to incompatible transfusions, Dr. Paton said that he had seen a woman only two weeks previously who underwent nephrectomy; her blood was of group A. She was given a transfusion of group O blood and developed hæmolytic jaundice that lasted for about a week. Dr. Paton said that he had seen many similar occurrences, and he agreed with Dr. Collins that it was a dangerous practice to give group O blood to people of group A if the right type of blood was available. Dr. Paton thought that when the typing of blood was done at night by resident medical officers, it should always be checked the following morning by members of the staff of the pathology department. At one hospital an example of gross incompatibility had occurred. A young woman was admitted to hospital with a severe hæmorrhage, and her blood was typed by the senior resident medical officer on duty, but her Rh status was not determined. She happened to be Rh-negative, and she was given Rh-positive blood. She derived some benefit from the transfusion, and left hospital, but returned some three months later with a similar hæmorrhage. The doctor on duty looked up her record, and thinking that she was Rh-positive, gave her some more Rh-positive blood, with disastrous results. She suffered anuria, and spent something like three or four months in the Clinical Research Unit at the Royal Prince Alfred Hospital—recovering in due course.

DR. EDGAR THOMSON said that the use of blood transfusion had been discussed and stressed on many occasions, and very adequately on the present occasion by the speakers; but there was abuse of blood transfusion. He spoke from a hospital in which one-fifth of the total amount of blood used in New South Wales was used, a good deal of it quite unnecessarily. In his opinion the greatest abuse was thoughtlessness on the part of surgeons and anæsthetists. Present-day surgeons embarked on enormous operations more and more frequently, and blood was ordered without any thought being given to the difficulty in donor supply. As Dr. Paton had said, to get blood for transfusion today, all that one had to do was to make a telephone call. Frequently the surgeon about to embark upon an operation ordered several pints of blood to be reserved. Frequently also, just because that blood had been reserved, it was given, not because it was needed, but because it was there. Dr. Thomson thought that surgeons might be a little more considerate, and so conserve the donor supply. He thought that the anæsthetist was now a double specialist—he gave anæsthetics and blood. That custom had grown up because for some extraordinary reason in the city of Sydney there were no such persons as transfusionists or specialists in intravenous therapy as there were in other centres. Dr. Thomson asked anæsthetists to advise the surgeons as to the necessity or otherwise of giving a blood transfusion. The anæsthetists were in a position to do so, because they were well informed on the maintenance of blood volume and electrolyte balance. Dr. Thomson had been surprised to hear Dr. Paton stress the fact that blood was given on the clinical condition of the patient. It was Dr. Thomson's experience that blood was often given on the hæmoglobin figure without consideration being given to the clinical indication.

Dr. Paton had spoken about the storage of blood too close to the refrigerator element, with the production of the buffy coat. Dr. Thomson thought that it was the duty of the medical officers, the anæsthetist, the pathologist, the physician and the surgeon to see that blood was properly cared for. It was not the duty of the nurses, who should not be expected to accept that responsibility. If the nurses were storing the blood too close to the refrigerator element, then it was high time that they were properly instructed by the medical officers responsible for transfusions. Dr. Thomson agreed that there was a lot of bad storage of blood, and so a lot of unnecessary waste. It was interesting that in all that had been said at the meeting about blood transfusion and the treatment of burns and other conditions of shock, no one had mentioned the word "albumin". Its administration was a very useful method of resuscitating patients suffering from shock or burns. He reminded those who had to treat such conditions that albumin achieved, in many cases, just as much as, and perhaps a lot more than, could be achieved by blood. Mention had been made of packed cells. It was very distressing frequently to see packed red cells ordered for a patient, and when they were delivered, to have the medical officer say that they were no longer wanted. This was a very good example of thoughtlessness. In conclusion, Dr. Thomson reminded the surgeons present that blood transfusion had not replaced and never would replace artery forceps.

DR. R. B. SPEIRS said that he had some pleasure in speaking, as he was the representative of the anæsthetists who had spoken at the meeting to which Dr. Thomson had referred, and at which the subject for discussion was chosen. The particular remark that had caused him to speak was that in the last year there had been so many thousands of bottles of blood used, and every bottle of it wasted. It had seemed to him that the anæsthetists would like to hear that proposition maintained. The blood bank and its bottles of blood had in his opinion kept a great deal of trouble from patients on whom extensive surgical operations were performed.

DR. R. J. WALSH spoke about the supply problem. He said that in recent years the social evolution had had some interesting features, not the least being the decline in the role of voluntary organizations in the community and their replacement in many instances by governmental instrumentalities. That had meant the virtual disappearance of the voluntary social worker in the community and the development of an attitude that the Government should provide. It was encouraging, and rather surprising, that the ever-increasing demands for blood had been met by voluntary donors. It was true to say that the great majority of blood donors were motivated by the highest ideals of service. They were particularly deserving of praise because they received no reward for their activities, and practically no recognition

at all. Dr. Walsh thought that the medical profession had a very serious responsibility to the blood donors to see that there was no wastage of their contributions, and that the best use was made of blood. One of the changes that had occurred in the practice of transfusion work was that there had been a separation of the organization for the obtaining of donors and for the collection of their blood from the organizations responsible for the administration of the blood. That change had had both disadvantages and advantages. On the credit side, it ensured a central reserve, it probably ensured greater safety in the collection and storage of blood, it ensured uniformity of technique and also in apparatus, it had given a wider range of specialized products such as the albumin that Dr. Thomson had mentioned, and theoretically it meant that it should reduce the wastage of blood. It also enabled the person who was giving the transfusion to commence the operation with a minimum of delay. On the other hand, under the present set-up those who administered transfusions were not easily able to appreciate the part that the donor played in a transfusion, unless they themselves acted as blood donors. There were some members of the medical profession who regularly made contributions; but the great majority of doctors who administered transfusions rationalized their failure to act as blood donors by saying that they could not spare the time. Dr. Walsh felt that if they more frequently acted as donors they would have more respect for the donors' contributions. It was indeed a fact that the ready availability of blood had resulted in a certain amount of abuse; it was an example of the dictum that what was obtained easily was very little respected. From the therapeutic point of view, wastage had been adequately dealt with by Dr. Collins and Dr. Fagan. However, there were two other serious points that needed to be raised. The first had been mentioned by Dr. Thomson—wastage due to negligence in the care and storage of blood by the person or persons responsible for giving transfusions. The second was what he (Dr. Walsh) would call donor wastage due to the medical profession. Referring to wastage due to negligence, Dr. Walsh said that it commonly happened that blood was ordered and for various reasons was not used. It was put aside in the refrigerator, usually a domestic refrigerator, and was then overlooked. After some days, weeks or months it was found; it could not be used for any purpose then, and was wasted. That was particularly common in private hospitals; unfortunately it also occurred in public hospitals, though not so frequently. It was a negligent practice which in Dr. Walsh's opinion was the most serious form of wastage of blood, and fatalities had resulted when such blood was given to patients. He had no doubt of what the voluntary donors would think if they heard of the prevalence of that negligence. Donor wastage by the medical profession was perhaps a more serious abuse in the field of transfusion. It had been established that, provided proper precautions were taken, the removal of blood at regular intervals did not harm healthy persons. No serious physician would dispute that fact; but unfortunately many practitioners in their rightful role of family consultants advised their patients not to become blood donors, or if they were blood donors and developed some quite unrelated symptoms, advised them to discontinue their activities. There was a widespread belief, even amongst the members of the medical profession, that many blood donors were unable adequately to replace blood that had been removed. Dr. Walsh thought that that delusion showed little faith in the extraordinary restorative powers of the hæmatopoietic system. There was also a delusion that any symptom occurring in a blood donor must be the result of giving blood. There was further a feeling that anæmia had replaced the operation wound as a social stigma, and any blood donor was considered to be anæmic. Unfortunately many blood donors were told that they were anæmic. In fact, in a recent survey in Sydney, 14 donors who had been told by their doctors that they were anæmic were investigated, and every one with one exception had a perfectly normal blood count, every known hæmatological test having been applied. Dr. Walsh thought that that was possibly the greatest deterrent to the population at large offering their services as blood donors—the lack of assurance from their medical advisers, firstly, of the necessity of their becoming blood donors, and secondly, that giving blood would do them no harm. From what had been said at the meeting, the papers could more profitably have been termed "the use and abuse of blood donors". Finally Dr. Walsh referred to Dr. Paton's remarks about the excessive use of blood causing the symptoms he had described in the peritoneal cavity and the suture points. Dr. Walsh thought that Dr. Paton had accurately described the clinical syndrome of fibrinolysis. He did not think it could be related to anticoagulants used in the blood. The physiological mechanism of fibrinolysis was activated by factors which he was sure were not connected with the transfusion; they were more connected with the surgical shock and with the hæmorrhage itself.

DR. F. A. E. LAWES said that he spoke as a physician, in case it should be thought that physicians did not waste blood. The temptation was very strong to use blood as a method of demonstrating one's skill to the patient's relatives. He had seen patients dying from diseases that were quite incurable, for whom a blood transfusion was ordered. The temptation was for the doctor to feel that he must do something, rather than tell the patient's friends that he was nearing the end of his life. Dr. Lawes said that he had seen a blood transfusion ordered for patients who were going to die shortly from acute leuchæmia or even from cancer, and he thought that way of using blood was entirely unjustifiable. He had been able to prevent his resident medical officer from giving blood transfusions by the method that Dr. Paton used—by seeing that the patient's bleeding had stopped and that he was going to recover. Whitby and Britton stated that a good indication for the withholding of blood was that the patient was having an adequate reticulocyte response and would not need blood.

DR. JAMES ISBISTER said that he wished to amplify Dr. Lawes's remarks. Dr. Isbister disagreed with Dr. Collins's statement that people with hæmatemesis and melæna on the whole did not receive sufficient blood transfusions. That might be so in relation to people who required transfusions; but Dr. Isbister was sure that many people with hæmatemesis and melæna did not require transfusions, and many who did not require them were getting transfusions at present. Dr. Isbister thought that often a transfusion was given after the hæmorrhage had stopped, when, given time, the patient would restore his own blood count to normal, as a means of getting the patient out of hospital more quickly and clearing a hospital bed. Very often the same applied when a patient would later require operation; the argument was that if a transfusion was given, the operation could be performed sooner. The patient should, of course, be discharged from hospital and readmitted a few weeks later for operation, if no hæmorrhage was taking place in the meantime. Dr. Isbister felt even more strongly on the subject of unnecessary blood transfusion since he was one of those who had given transfusions in pre-Rh days. They saw reactions occur, they did not know why, and only subsequently had they discovered that Rh incompatibility was the cause and untold harm had been done as a result, particularly to women. The question of pyrogenic reactions had been mentioned. Dr. Isbister said that at present they very often saw people develop a transfusion pyrexia and have a rigor, and the general opinion was that it was a pyrogen reaction and that the blood was compatible. In his opinion some of those reactions might not be pyrogen reactions. The question of blood grouping was very complex, and it seemed to him that there must be minor incompatibilities which were not detected by the ordinary methods, and which might possibly account for some of the so-called pyrogenic reactions. After all, transfusionists were administering foreign protein, foreign platelets and so on, and unless a transfusion was really indicated, then to give one might be doing the patient a disservice and causing harm later. As hæmolytic disease of the newborn had occurred many years after an incompatible transfusion to the mother, surely some of the peculiar diseases seen in increasing numbers at the present time might possibly be related to unknown incompatibilities of blood transfusion. Dr. Isbister agreed with Dr. Collins that transfusion in many cases of anæmia was unnecessary. Dr. Collins had said that it was essential first to decide whether the patient had anæmia. Another aspect of the problem which Dr. Isbister often met was presented by the patient who was sent to hospital after having received liver injections, vitamin B_{12} injections, iron by mouth and iron injections, and was still anæmic; the patient was sent into hospital for blood transfusion. Obviously the problem called for diagnosis, and often an adequate history would provide the solution. Dr. Isbister believed that too often anæmic patients received blood transfusions just because they were not getting better with simpler forms of treatment.

DR. MAX LAKE asked whether the citrate anticoagulant used in blood for transfusion was as safe as had been claimed. The question was prompted by the observation that patients who received large quantities of blood, perhaps in excess of 20 pints during the treatment of acute hæmorrhage, failed to respond to transfusion as expected, that "all the good had gone out of them". Dr. Lake wondered whether the large quantities of citrate mentioned by Dr. Paton might have a deleterious effect. He asked whether it was possible to give a sufficiently small dose of heparin to avoid interference with the post-operative course and yet be an efficient anticoagulant.

DR. ALAN SHARP, commenting on the value of heparin in intravenous therapy, said that in his experience it could be employed with advantage to inhibit vein thrombosis locally by the injection of four minims of a solution containing 5000 units per cubic centimetre into the tubing just proximal to the needle. That could be done perhaps every eight hours after the beginning of the transfusion, so as to keep the vein from becoming too irritated. It had practically no general anticoagulant effect, and was not likely to be deleterious. There was no place for introducing heparin into a transfusion in large quantities. Dr. Sharp then said that he had two points to discuss. The first was a plea for the avoidance of giving transfusions of any kind into the legs. There were always plenty of veins in the arm. Transfusion into the leg veins predisposed the patient to the subsequent development of a thrombosis. The second point related to the question of freezing. The dangers of freezing blood had been pointed out during the meeting. Recently at Sydney Hospital a point was raised when the freezing of a patient was contemplated; during the course of pre-operative investigations, cold agglutinins were demonstrated in the patient's blood. Freezing was therefore not employed because it was considered possible that hæmolytic reactions might arise.

DR. S. V. MARSHALL asked whether any of those present had recently noticed a greatly increased incidence of thrombophlebitis or phlebothrombosis or periphlebitis in connexion with blood transfusions and intravenous saline therapy. He thought it might have something to do with the rubber tubing used.

Dr. Fagan, in reply, said that he agreed strongly with Dr. Paton that the clinical signs were the guide to the patient's need for blood. He did not agree that transfusion was either a useful or an economical method of restoring blood protein levels. In reply to Dr. Thomson, Dr. Fagan said that surgeons were surely justified in estimating the need for pre-operative transfusions from the hæmoglobin value. Concentrated albumin was not readily available at present. Dr. Fagan was grateful to Dr. Walsh for uncovering a number of abuses of which he had not been aware. Dr. Walsh's information on fibrinolysis was new to him, and valuable. Dr. Fagan agreed strongly with Dr. Lawes that the giving of transfusions to moribund patients was a grave abuse, and with what Dr. Isbister had said about hæmatemesis. Dr. Fagan thanked Dr. Sharp for his information about heparin. He agreed with Dr. Marshall that there was a high incidence of thrombosis in veins used for intravenous therapy; he was himself inclined to attribute it to the very prolonged nature of such treatment at the present time, but appreciated Dr. Marshall's opinion that it might be something to do with the rubber.

Dr. Collins, in reply to Dr. Isbister's remarks about hæmatemesis, said that he agreed that many people received unnecessary transfusions for that condition. On the other hand, people who needed transfusions were in his opinion given insufficient blood. If a patient lost a litre of blood by hæmatemesis, he should be given a litre of blood. How was one to tell whether that patient had not an erosion of an artery, and was therefore likely to lose another litre of blood shortly? If that happened, the patient would become shocked and the state of shock might become irreversible. On the other hand, if the patient had had a mild hæmatemesis and was in good condition and did not appear to have lost very much blood, it was a waste of time to give him a transfusion. With regard to minute incompatibilities, Dr. Collins said that there were various degrees of severity of intergroup reactions. If a patient of group A was given group B blood, he might have a mild anti-B reaction or no reaction might occur. On the other hand, he might have active hæmolysis and the blood would be eliminated very rapidly. The patient might have a very severe reaction from incompatibility; on the other hand, he might appear well, the blood volume would be restored, he would feel better, the blood pressure would rise, but over the period of a few days he might become mildly jaundiced and the transfused blood would be eliminated over the course of a week. Dr. Collins thought that that happened not infrequently. In reply to Dr. Lake's question whether the goodness went out of blood, Dr. Collins said that he did not think the transfusion of large quantities of citrated blood had any effect from the point of view of the citrate. If the patient's blood was to become incoagulable as the result of citrate, one would expect the patients to have a lower serum calcium level and to develop tetany, which did not occur. The liver was capable of metabolizing citrate very rapidly as part of the Krebs cycle. It was virtually impossible to overload the body with citrate in the form of transfused blood. Another question concerned the viability of clotting factors in stored blood. Work had been done recently in that connexion at the Red Cross, because it had been stated that fresh blood was more valuable than stored blood. Dr. Collins said that the only important clotting factor that was lost in storage was the antihæmophilic factor; according to in-vitro testing it fell to about 50% of its level within a period of about eight days. However, no one would ever give a hæmophiliac anything but fresh blood. The in-vitro tests seemed fairly conclusive, and the same applied to Factor V, which fell to about half its level in about a week. Prothrombin, Factor VII, and presumably Christmas factor, were present in virtually normal amounts at the end of about a fortnight. Dr. Collins did not think that the administration of blood would perpetuate hæmorrhage because of lack of any clotting factor, or because of its citrate content.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

HIGH COST OF LIVING IN 1810.[1]

[From the letters of Joseph Arnold, M.D., F.L.S., February 25, 1810.]

IN this town the greatest extravagance prevails. You cannot spend the day at an inn under 2 or 3 guineas. But still the people who are settlers here give the most sumptuous dinners, sticking at no expense. Many of them when they have a friend or two going to see them, will give a guinea for a turkey and as much for a dish of fruit. What the officers of the 73rd will do I cannot tell. Scarcely one of them has more than his pay, and I was told that the expense of the mess for ten days comes to £45.

I would bring many curiosities home with me, could they be had. But they charge so much for them that it would be idle to purchase them, unless with rum, which I unfortunately have none of. They often for a parrot, a kangaroo, a few shells or an opossum will ask £5 and will take a gallon of rum instead which actually was bought at the Cape of Good Hope for 6 shillings. Our first lieutenant was fortunate enough to bring a hogshead of it: and consequently has filled the ship with kangaroos, parrots of different kinds, opossums, flying squirrels, shells &c. We only can get things cheaply of the Indians who bring corals, shells &c and are glad to take old clothes, biscuits and wine for them.

Correspondence.

THE TREATMENT OF CANCER IN NEW SOUTH WALES.

SIR: In the editorial in the issue of your journal of January 8, 1944, calling for a new outlook and new organization of cancer treatment, the words of a distinguished cancer specialist, who had just visited Australia at the request of the New South Wales Government, were quoted as follows: ". . . at the present time enough is known, if available knowledge is thoroughly and promptly applied, to alter the state of affairs very greatly in a number of types of cancer." The editorial ended with the words: "Australia should not lag behind other countries in cancer treatment."

Two other States in Australia took heed, and have since then developed modern cancer institutes. New South Wales still lags years behind, particularly in the organization of radiotherapy services.

It is still true today that the methods available for possible cure of cancer are two only, surgery and radiotherapy (including X-ray therapy, radium and radioactive isotopes). Chemotherapy and hormone therapy, which are used daily by surgeons and radiotherapists in Sydney, are still essentially palliative, and no new method of cure appears just around the corner.

[1] From the original in the Mitchell Library, Sydney.

The problem still is, and will remain for years to come, to provide efficient and modern treatment for the thousands of new cancer patients presenting yearly for treatment in this State. It is a big problem, but much could have been done in the years that have gone since your editorial. The responsibility for the parlous position here must rest fairly and squarely on the shoulders of the New South Wales Government and the Hospitals Commission of this State.

The fact seems to have been lost sight of by some in New South Wales that radiotherapy is an important method of cancer treatment; and is, in fact, used in more cases than surgery, although the two are often used in combination.

A recent survey of the general care of cancer patients at two of the main teaching hospitals in Sydney showed that approximately 40% of the patients attending for deep X-ray therapy were receiving inadequate care. There are not enough beds for deep X-ray patients who require hospitalization, nor is there any suitable accommodation close to treatment centres for ambulatory patients who require this. Many patients who have a reasonable chance of cure by modern radiotherapy have their chances jeopardized by being forced to attend from long distances as out-patients. Cases of malignant disease of the abdomen, upper respiratory tract, skull and thyroid should always be admitted to hospital, while those with cancer of the pelvis, lungs and many other sites should be under constant nursing care while having treatment and should rest in bed as much as possible. These things, however, are rarely achieved in Sydney under the present state of affairs.

One might also mention that at one leading hospital, in the deep X-ray department, there are no changing cubicles for the patients; public patients, ambulance cases and others must wait in a cold and draughty corridor, and not infrequently ambulance cases have had to wait a matter of hours for the ambulance to return for them. A special ambulance service for cancer patients is an obvious necessity, and, of course, ample beds and a hostel service. All these facts are well known to the Hospitals Commission (or should be), as they were discussed at great length some twelve years ago by a committee of which I was a member, and recommendations were made for urgent action. One teaching hospital in Sydney has no deep X-ray facilities at all and, despite repeated requests for it over years, has received no satisfaction from the Hospitals Commission.

Several world-renowned experts on cancer treatment have visited Sydney, and have advised the Government on cancer services. Professor Windeyer, of London, who is adviser to the British Ministry of Health on radiotherapy services, referred in 1951 to Sydney's radiotherapy services as "inadequate, obsolete and in need of reorganization". Professor McWhirter, of Edinburgh, in 1954, and recently Sir Stanford Cade and Professor Windeyer, when in Sydney, spoke in strong terms of the need for reorganization, provision of beds, adequate modern equipment and the appointment of physicists—confirming the recommendations the Government had already received from its own cancer committees on more than one occasion. Each of these experts answered long lists of questions by the Cancer Council and its committees.

Several of the senior radiotherapists in Sydney have had considerable overseas experience, and have, in fact, been members of the staff of leading radiotherapy centres in Great Britain for long periods. Two of them had extensive overseas trips recently, at their own expense, one in 1952 and one in 1953. Their knowledge has been made available to the Government in reports.

Recently I read in the public Press that the Government had approved of a trip overseas by Dr. A. B. Lilley, to study the construction and equipment of cancer institutes in Britain, Sweden, United States and Canada, and he would probably go next year. I presume he will write a further report on his return, and this will be considered in due course by the Cancer Council and the Government, with a further delay of years in the provision of just facilities for cancer sufferers. This proposed trip would be a waste of money and, far more seriously, a waste of time. The money expended would be better used in providing relief in the transport of cancer patients to hospitals, or to obtain a first-class radiological physicist from Great Britain, and pay his salary for a year or so.

Dr. Lilley, with all due respect, has not been trained in the modern radiotherapy of cancer, and it is monstrous that we should be asked to wait for another long period for an opinion from him, after another trip abroad, when world experts have already expressed quite clearly what should be done in Sydney.

Supervoltage equipment has been ordered in three other Australian States, and is, in fact, about to be installed in Melbourne. I already have personal experience of some patients who have had to go to England for this treatment; and shortly I shall be forced to send some to other States for a similar reason. Supervoltage apparatus should have been ordered for Sydney some time ago.

It is a fact that on the New South Wales State Cancer Council and its two committees there is no radiological physicist, and in view of the vast amount of work being done in atomic physics as applied to medicine (including radioactive isotopes and supervoltage) and its likely development in the future, this appears distinctly anomalous. The position is far different in other Australian States. The New South Wales Branch of the College of Radiologists of Australasia pointed this out to the Minister of Health in 1952, but without avail.

As a senior radiotherapist, and one who has to deal with many cancer patients, I find the position over the years becoming more and more frustrating.

Is it any wonder, under the present conditions, that we find it difficult to attract an adequate number of able medical graduates to the specialty of radiotherapy?

Yours, etc.,

135 Macquarie Street,
Sydney,
November 15, 1955.

HAROLD J. HAM.

UNEXPLAINED DEATHS UNDER ANÆSTHESIA.

SIR: It would be appreciated if any reader of THE MEDICAL JOURNAL OF AUSTRALIA who has had a completely unexplained anæsthetic death would communicate the circumstances to me. The type of patient should be one who is an "A" class risk, the operation one not involving shock or hæmorrhage, and the anæsthetic one which was correctly chosen, and in the administration of which there were no difficulties.

Information is also desired on the presence of any congenital defects (no matter how small), and whether a sudden increase in the concentration of anæsthetic vapour had immediately preceded the cardiac arrest. (Obviously a number of these cases would have been resuscitated and no post-mortem results would be available.)

It is hoped to collect a series of such cases and ascertain if there is any feature common to them (such as congenital defects *et cetera*).

Yours, etc.,

342 Albert Street,
East Melbourne,
Victoria.
November 10, 1955.

W. H. J. COLE.

THE TEACHING OF SURGERY.

SIR: I would like to comment on several of the points raised in the discussion in the Section of Surgery on the very important question of the teaching of surgery to undergraduates (M. J. AUSTRALIA, October 22, 1955).

Dr. Lendon, the President, has expressed the opinion that "in teaching surgery to undergraduates the aim was to enable them to recognize the common surgical conditions, to treat the minor conditions adequately and to perform the common emergency operations". This is most admirable, but the question is: how is it to be achieved?

The methods of teaching students are: (i) by means of lectures, (ii) by work in the wards and out-patient departments, (iii) by specially arranged demonstrations, (iv) by the method of tutorial instruction.

There are very great difficulties in arranging this teaching; but unless it is well arranged, the quality of the teaching suffers. Nowadays, is it not a fact that the training of undergraduates in some medical schools is subordinated to an undue degree to the routine work of the hospital and to the training of those who aspire to higher degrees in surgery?

Forty years ago the training offered to students at Sydney Hospital was indeed very good. The lecturer in clinical surgery delivered lectures twice weekly on some aspect of surgery, bringing the patients to the lecture room.

Teachers of surgery in the Queensland Medical School were recently privileged to hear from Sir James Learmonth his views on the teaching of surgery, and he addressed the students on the points which should be brought out in a clinical lecture. I was fortunate in being able to hear lectures on clinical surgery by the late Sir Herbert Maitland in which he made the points that were enlarged upon by Sir James Learmonth.

Clinical lectures can be used for the instruction of large classes, and they provide an opportunity to guide students in the correct management of patients, and emphasize in a practical manner the principles which should be followed. Sir Herbert Maitland was an adept at this art, and to this day I remember very clearly his lecture on the treatment of intestinal obstruction.

At Sydney Hospital the teaching of tutorial surgery, which preceded clinical work, was looked upon as most important and necessary before students entered the wards. This instruction was given by a senior member of the visiting honorary medical staff. Another important part of the teaching was that given to individuals or small groups of students by senior members of the resident medical staff. In general, the great majority of members of the hospital medical staff did their best to instruct students, and to teach them to think and act correctly on sound lines.

Whilst I was in England in 1919 I had the privilege of studying at first hand teaching methods in London. This was very well done, but there were a few teachers who seemed to delight in bullying students, or in making them look stupid. This method would not be suitable in Australia. Students who are thus handled are prevented from doing themselves justice. It is a method of teaching which does not give the best results.

I would like to point out that constant discussions on the faults of the curriculum have led over the years to great improvements, and I cannot agree with Dr. Konrad Hirschfeld that this leads to students regarding themselves as "very ill-used".

Dr. Lendon has stressed the importance of the teaching of minor surgery. This is very badly done in some hospitals. At Sydney Hospital it was the practice to arrange for minor surgery to be done each morning, and students had the opportunity of attending for instruction.

Surgery is required for many patients, and the quality of the service rendered should be first class. This aspect of the problem in Australia has not received the consideration it deserves. That the standard is as high as it is can be largely ascribed to the native intelligence and ability of our students.

Yours, etc.,

Brisbane, November 5, 1955.

E. S. MEYERS.

ADRENALECTOMY IN METASTATIC BREAST CANCER: A REPORT OF SIX CASES.

SIR: In the paper by Mr. W. E. A. Hughes-Jones on "Adrenalectomy in Metastatic Breast Cancer: A Report of Six Cases" the beneficial changes which the operation produces during the remainder of the life of most patients do not receive sufficient emphasis.

When first encountered, the relief of pain which often follows immediately after the adrenalectomy seems miraculous. In addition, this relief from pain may be accompanied by considerable improvement in the mental and physical state of the patient. Similar changes in the symptoms have also been reported following hypophysectomy, but we have no simpler means at our disposal for producing anything like this effect.

It is agreed with Mr. Hughes-Jones that the relentless progression of the disease may be unaffected by removal of the adrenal glands and ovaries; but, even if this applied to all cases, and there is some doubt about that, does he mean that there is no place for adrenalectomy in the management of metastatic breast cancer? Was not the relief from the pain of the vertebral metastases a boon to his fifth case?

Having seen the great changes in the comfort, well-being and mental attitude of my patients after bilateral adrenalectomy and oophorectomy, I believe that, until something better is found, this procedure deserves a bigger rather than a smaller place in the palliation of these cases.

However, the technical problems of this operation and its after-care are greater from the anæsthetic point of view

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED NOVEMBER 5, 1955.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	5(3)	1(1)	3	..	2(1)	..	1	..	12
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	2	..	..	..	..	..	1	..	3
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	1	1	..	..	..	..	..	2
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	1(1)	..	..	..	..	..	..	1
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	14(11)	17(14)	11(8)	..	..	..	..	..	42
Diphtheria	1	6(6)	1	..	4(1)	..	..	..	12
Dysentery (Bacillary)	..	..	1	10(4)	..	..	..	..	11
Encephalitis	..	1	..	1(1)	..	..	..	..	2
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	61(32)	91(37)	..	18(8)	8(5)	4	..	..	182
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	7	..	..	..	..	..	7
Malaria	..	..	1	..	..	..	1	..	2
Meningococcal Infection	2(1)	..	..	..	..	2	..	..	4
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	3(1)	..	1	10(8)	..	..	..	..	14
Puerperal Fever	1	..	..	..	..	..	..	..	1
Rubella	..	155(47)	..	5(3)	..	..	..	..	160
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	12(5)	36(25)	20(7)	5(3)	1(1)	..	..	..	74
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	..	..	..	..	..
Trachoma	..	..	..	..	82	..	..	..	82
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	41(31)	24(15)	20(9)	8(4)	8(6)	2	1	..	104
Typhoid Fever	..	1(1)	1(1)	..	..	..	..	..	2
Typhus (Flea-, Mite- and Tick-borne)	..	..	1	..	..	..	..	..	1
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

than from the surgical, and it must be stressed that the services of a specialist anæsthetist especially interested and skilled in these anæsthetics are essential.

Yours, etc.,

159 Macquarie Street, Sydney, November 9, 1955. EDWARD WILSON.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Lecture at the Balmoral Naval Hospital.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that Dr. C. H. Wickham Lawes will give a lecture entitled "Varicose Veins" on Tuesday, December 6, 1955, at the Balmoral Naval Hospital at 2 p.m. Clinical cases will be shown after the lecture. Members of the medical profession and senior medical students are invited to attend.

Public Health.

REGULATIONS UNDER THE POLICE OFFENCES (AMENDMENT) ACT, 1908.

THE following amendment to the Regulations under the *Police Offences (Amendment) Act*, 1908, has been promulgated in the *New South Wales Government Gazette* of November 18, 1955:

The Regulations under the Police Offences (Amendment) Act, 1908, as amended by subsequent Acts, are amended:

(*a*) By inserting in paragraph (1) of Regulation 11 after the word "transaction" the words: "Each such entry shall, inter alia, in the column provided in the register for the particular purpose—

(*a*) show the balance of the drug held by the holder of a licence or other authorized person, at the premises where the register is kept, after the transaction to which the entry relates;

(*b*) be signed, on the day the entry is made, by the actual dispenser or administrator of the drug."

(*b*) By omitting Regulations 12 and 13 and the heading thereto.

(*c*) By omitting the words "(One only, irrespective of strength, to page)" in Schedule 5 and inserting in lieu thereof the words "(One drug, of one trade name and one strength only to page)".

Medical Appointments.

Dr. T. V. Stubbs Brown (nominated by the Queensland Branch of the British Medical Association, recognized by the Minister as representative of medical practitioners) has been appointed a member of the Medical Board of Queensland.

Dr. W. A. A. G. Macbeth has been appointed surgical registrar at the Royal Adelaide Hospital, South Australia.

Dr. D. R. E. Tandy and Dr. E. B. Grinsted have been appointed medical officers, on probation for a period of six months, in the Department of Public Health, New South Wales.

Nominations and Elections.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association: Bray, John Wilkinson, M.B., B.S., 1955 (Univ. Sydney); Clarkson, Joan Violet, M.B., B.S., 1955 (Univ. Sydney); Whitehouse, Cornelia Anne, M.B., B.S., 1955 (Univ. Sydney); *Christie, Gwenda Joy, M.B., B.S., 1954 (Univ. Sydney)*; Patterson, Robert William, M.B., B.S., 1954 (Univ. Sydney).

Deaths.

THE following death has been announced:

ADRIAN.—Joseph Adrian, on November 13, 1955, at Melbourne, Victoria.

Diary for the Month.

DEC. 1.—*New South Wales Branch, B.M.A.: Clinical Meeting.*
DEC. 6.—New South Wales Branch, B.M.A.: Organization and Science Committee.
DEC. 7.—Western Australian Branch, B.M.A.: Branch Council.
DEC. 7.—Victorian Branch, B.M.A.: Branch Meeting.
DEC. 7.—Victorian Branch, B.M.A.: Branch Council.
DEC. 8.—New South Wales Branch, B.M.A.: Branch Meeting.
DEC. 9.—*Tasmanian Branch, B.M.A.: Branch Council.*
DEC. 12.—Victorian Branch, B.M.A.: Executive of Branch Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all contract practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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